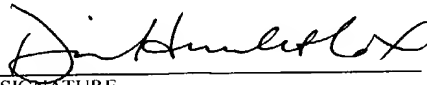


FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER PF-0681 USN
		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) TO BE ASSIGNED 09/937059
INTERNATIONAL APPLICATION NO PCT/US00/07817	INTERNATIONAL FILING DATE 22 March 2000	PRIORITY DATE CLAIMED 22 March 1999
TITLE OF INVENTION HUMAN TRANSMEMBRANE PROTEINS		
APPLICANT(S) FOR DO/EO/US INCYTE PHARMACEUTICALS, INC.; YUE, Henry; LAL, Preeti; TANG, Y. Tom; HILLMAN, Jennifer L.; REDDY, Roopa; BANDMAN, Olga; BAUGHN, Mariah R.; LU, Dyung Aina M.; AZIMZAI, Yalda; YANG, Junming		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information: 1. <input checked="" type="checkbox"/> This is the FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input type="checkbox"/> This is an express request to promptly begin national examination procedures (35 U.S.C. 371 (f)). 4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (PCT Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau) b. <input type="checkbox"/> has been communicated by the International Bureau. c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).		
Items 11 to 16 below concern document(s) or information included: 11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.27 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment, as follows: Cancel in this application original claims 16, 19 & 22 before calculating the filing fee, without prejudice or disclaimer. Applicants submit that these claims were included in the application as filed in the interest of providing notice to the public of certain specific subject matter intended to be claimed, and are being canceled at this time in the interest of reducing filing costs. Applicants expressly state that these claims are not being canceled for reasons related to patentability, and are in fact fully supported by the specification as filed. Applicants expressly reserve the right to reinstate these claims or to add other claims during prosecution of this application or a continuation or divisional application. Applicants expressly do not disclaim the subject matter of any invention disclosed herein which is not set forth in the instantly filed claims. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input type="checkbox"/> A change of power of attorney and/or address letter. 16. <input checked="" type="checkbox"/> Other items or information: 1) Transmittal Letter (2 pp, in duplicate) 2) Return Postcard 3) Express Mail Label No.: EL 856 147 675 US 4) Request to Transfer		

U.S. APPLICATION NO. (if known see 37 CFR 1.53) 09/937059		INTERNATIONAL APPLICATION NO. PCT/US00/07817		ATTORNEY'S DOCKET NUMBER PF-0681 USN	
<p>17. <input checked="" type="checkbox"/> The following fees are submitted</p> <p>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):</p> <p>Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ... \$1000.00</p> <p><input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO...\$860.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$710.00</p> <p><input checked="" type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)).....\$690.00</p> <p><input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)).....\$100.00</p>					
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$690.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	20 =	0	X \$ 18.00	\$	
Independent Claims	2 =	0	X \$ 80.00	\$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$270.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$	
<input type="checkbox"/> Applicant claims small entity status See 37 CFR 1.27 The fees indicated above are reduced by 1/2				\$	
SUBTOTAL =				\$690.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f))				\$	
TOTAL NATIONAL FEE =				\$690.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by the appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$	
TOTAL FEES ENCLOSED =				\$690.00	
				Amount to be Refunded:	\$
				Charged	\$
<p>a. <input type="checkbox"/> A check in the amount of \$_____ to cover the above fees is enclosed.</p> <p>b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. 09-0108 in the amount of \$690.00 to cover the above fees.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 09-0108. A duplicate copy of this sheet is enclosed.</p> <p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</p> <p>SEND ALL CORRESPONDENCE TO:</p> <p>INCYTE GENOMICS, INC. 3160 Porter Drive Palo Alto, CA 94304</p> <p style="text-align: center;"> SIGNATURE</p> <p style="text-align: center;">NAME: Diana Hamlet-Cox</p> <p style="text-align: center;">REGISTRATION NUMBER 33,302</p> <p style="text-align: center;">DATE: 12 September 2001</p>					

HUMAN TRANSMEMBRANE PROTEINS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of human transmembrane
5 proteins and to the use of these sequences in the diagnosis, treatment, and prevention of cell
proliferative, immunological, reproductive, smooth muscle, and neurological disorders.

BACKGROUND OF THE INVENTION

Eukaryotic organisms are distinct from prokaryotes in possessing many intracellular
10 membrane-bound compartments such as organelles and vesicles. Many of the metabolic reactions
which distinguish eukaryotic biochemistry from prokaryotic biochemistry take place within these
compartments. In particular, many cellular functions require very stringent reaction conditions, and
the organelles and vesicles enable compartmentalization and isolation of reactions which might
otherwise disrupt cytosolic metabolic processes. The organelles include mitochondria, smooth and
15 rough endoplasmic reticula, sarcoplasmic reticulum, and the Golgi body. The vesicles include
phagosomes, lysosomes, endosomes, peroxisomes, and secretory vesicles. Organelles and vesicles
are bounded by single or double membranes.

Biological membranes surround organelles, vesicles, and the cell itself. Membranes are
highly selective permeability barriers made up of lipid bilayer sheets composed of phosphoglycerides,
20 fatty acids, cholesterol, phospholipids, glycolipids, proteoglycans, and proteins. Membranes contain
ion pumps, ion channels, and specific receptors for external stimuli which transmit biochemical
signals across the membranes. These membranes also contain second messenger proteins which
interact with these pumps, channels, and receptors to amplify and regulate transmission of these
signals.

25 Plasma Membrane Proteins

Plasma membrane proteins (MPs) are divided into two groups based upon methods of protein
extraction from the membrane. Extrinsic or peripheral membrane proteins can be released using
extremes of ionic strength or pH, urea, or other disruptors of protein interactions. Intrinsic or integral
membrane proteins are released only when the lipid bilayer of the membrane is dissolved by
30 detergent.

The majority of known integral membrane proteins are transmembrane proteins (TM) which
are characterized by an extracellular, a transmembrane, and an intracellular domain. TM domains are
typically comprised of 15 to 25 hydrophobic amino acids which are predicted to adopt an α -helical
conformation. TM proteins are classified as bitopic (Types I and II) and polytopic (Types III and IV)
35 (Singer, S.J. (1990) Annu. Rev. Cell Biol. 6:247-96). Bitopic proteins span the membrane once while

WO 00/56891

PCT/US00/07817

polytopic proteins contain multiple membrane-spanning segments. TM proteins carry out a variety of important cellular functions acting as cell-surface receptor proteins involved in signal transduction. These functions are represented by growth and differentiation factor receptors, and receptor-interacting proteins such as Drosophila pecanex and frizzled proteins, LIV-1 protein, NF2 protein, and GNS1/SUR4 eukaryotic integral membrane proteins. TM proteins also act as transporters of ions or metabolites, such as gap junction channels (connexins), and ion channels, and as cell anchoring proteins, such as lectins, integrins, and fibronectins. TM proteins are found in vesicle organelle-forming molecules, such as caveolins; or cell recognition molecules, such as cluster of differentiation (CD) antigens, glycoproteins, and mucins.

Many MPs contain amino acid sequence motifs that serve to localize proteins to specific subcellular sites. Examples of these motifs include PDZ domains, KDEL, RGD, NGR, and GSL sequence motifs, von Willebrand factor A (vWFA) domains, and EGF-like domains. RGD, NGR, and GSL motif-containing peptides have been used as drug delivery agents in targeted cancer treatment of tumor vasculature (Arap, W. et al. (1998) Science, 279:377-380). Furthermore, MPs may also contain amino acid sequence motifs that serve to interact with extracellular or intracellular molecules, such as carbohydrate recognition domains (CRD).

Chemical modification of amino acid residue side chains alters the manner in which MPs interact with other molecules, for example, phospholipid membranes. Examples of such chemical modifications to amino acid residue side chains are covalent bond formation with glycosaminoglycans, oligosaccharides, phospholipids, acetyl and palmitoyl moieties, ADP-ribose, phosphate, and sulphate groups.

RNA encoding membrane proteins may have alternative splice sites which give rise to proteins encoded by the same gene but with different messenger RNA and amino acid sequences. Splice variant membrane proteins may interact with other ligand and protein isoforms.

G-Protein Coupled Receptors

G-protein coupled receptors (GPCRs) are a superfamily of integral membrane proteins which transduce extracellular signals. GPCRs include receptors for biogenic amines, lipid mediators of inflammation, peptide hormones, and sensory signal mediators. The structure of these highly-conserved receptors consists of seven hydrophobic transmembrane (serpentine) regions, cysteine disulfide bridges between the second and third extracellular loops, an extracellular N-terminus, and a cytoplasmic C-terminus. Three extracellular loops alternate with three intracellular loops to link the seven transmembrane regions. The most conserved parts of these proteins are the transmembrane regions and the first two cytoplasmic loops. A conserved, acidic-Arg-aromatic residue triplet present in the second cytoplasmic loop may interact with G proteins. A GPCR consensus pattern is characteristic of most proteins belonging to this superfamily

WO 00/56891

PCT/US00/07817

(ExPASy PROSITE document PS00237; and Watson, S. and S. Arkinstall (1994) The G-protein Linked Receptor Facts Book, Academic Press, San Diego, CA, pp 2-6). Mutations and changes in transcriptional activation of GPCR-encoding genes have been associated with neurological disorders such as schizophrenia, Parkinson's disease, Alzheimer's disease, drug addiction, and feeding disorders.

Scavenger Receptors

Macrophage scavenger receptors with broad ligand specificity may participate in the binding of low density lipoproteins (LDL) and foreign antigens. Scavenger receptors types I and II are trimeric membrane proteins with each subunit containing a small N-terminal intracellular domain, a transmembrane domain, a large extracellular domain, and a C-terminal cysteine-rich domain. The extracellular domain contains a short spacer domain, an α -helical coiled-coil domain, and a triple helical collagenous domain. These receptors have been shown to bind a spectrum of ligands, including chemically modified lipoproteins and albumin, polyribonucleotides, polysaccharides, phospholipids, and asbestos (Matsumoto, A. et al. (1990) Proc. Natl. Acad. Sci. USA 87:9133-9137; and Elomaa, O. et al. (1995) Cell 80:603-609). The scavenger receptors are thought to play a key role in atherogenesis by mediating uptake of modified LDL in arterial walls, and in host defense by binding bacterial endotoxins, bacteria, and protozoa.

Tetraspan Family Proteins

The transmembrane 4 superfamily (TM4SF) or tetraspan family is a multigene family encoding type III integral membrane proteins (Wright, M.D. and Tomlinson, M.G. (1994) Immunol. Today 15:588). The TM4SF is comprised of membrane proteins which traverse the cell membrane four times. Members of the TM4SF include platelet and endothelial cell membrane proteins, melanoma-associated antigens, leukocyte surface glycoproteins, colonic carcinoma antigens, tumor-associated antigens, and surface proteins of the schistosome parasites (Jankowski, S.A. (1994) Oncogene 9:1205-1211). Members of the TM4SF share about 25-30% amino acid sequence identity with one another. A number of TM4SF members have been implicated in signal transduction, control of cell adhesion, regulation of cell growth and proliferation, including development and oncogenesis, and cell motility, including tumor cell metastasis. Expression of TM4SF proteins is associated with a variety of tumors and the level of expression may be altered when cells are growing or activated.

Tumor Antigens

Tumor antigens are surface molecules that are differentially expressed in tumor cells relative to normal cells. Tumor antigens distinguish tumor cells immunologically from normal cells and provide diagnostic and therapeutic targets for human cancers (Takagi, S. et al. (1995) Int. J. Cancer 61: 706-715; Liu, E. et al. (1992) Oncogene 7: 1027-1032).

35

WO 00/56891

PCT/US00/07817

Ion Channels

Ion channels are found in the plasma membranes of virtually every cell in the body. For example, chloride channels mediate a variety of cellular functions including regulation of membrane potentials and absorption and secretion of ions across epithelial membranes. When present in intracellular membranes of the Golgi apparatus and endocytic vesicles, chloride channels also regulate organelle pH. (See, e.g., Greger, R. (1988) *Annu. Rev. Physiol.* 50:111-122.) Electrophysiological and pharmacological properties of chloride channels, including ion conductance, current-voltage relationships, and sensitivity to modulators, suggest that different chloride channels exist in muscles, neurons, fibroblasts, epithelial cells, and lymphocytes. Many channels have sites for phosphorylation by one or more protein kinases including protein kinase A, protein kinase C, tyrosine kinase, and casein kinase II, all of which regulate ion channel activity in cells. Inappropriate phosphorylation of proteins in cells has been linked to changes in cell cycle progression and cell differentiation. Changes in the cell cycle have been linked to induction of apoptosis or cancer. Changes in cell differentiation have been linked to diseases and disorders of the reproductive system, immune system, and skeletal muscle.

Proton Pumps

Proton ATPases are a large class of membrane proteins that use the energy of ATP hydrolysis to generate an electrochemical proton gradient across a membrane. The resultant gradient may be used to transport other ions across the membrane (Na^+ , K^+ , or Cl^-) or to maintain organelle pH. Proton ATPases are further subdivided into the mitochondrial F-ATPases, the plasma membrane ATPases, and the vacuolar ATPases. The vacuolar ATPases establish and maintain an acidic pH within various vesicles involved in the processes of endocytosis and exocytosis (Mellman, I. et al. (1986) *Ann. Rev. Biochem.* 55:663-700). Proton-coupled, 12 membrane-spanning domain transporters such as PEPT 1 and PEPT 2 are responsible for gastrointestinal absorption and for renal reabsorption of peptides using an electrochemical H^+ gradient as the driving force. Another type of peptide transporter, the TAP transporter, is a heterodimer consisting of TAP 1 and TAP 2 and is associated with antigen processing. Peptide antigens are transported across the membrane of the endoplasmic reticulum by TAP so they can be expressed on the cell surface in association with MHC molecules. Each TAP protein consists of multiple hydrophobic membrane spanning segments and a highly conserved ATP-binding cassette (Boll, M. et al. (1996) *Proc. Natl. Acad. Sci. USA* 93:284-289). Pathogenic microorganisms, such as herpes simplex virus, may encode inhibitors of TAP-mediated peptide transport in order to evade immune surveillance (Marusina, K. and Manaco, J.J. (1996) *Curr. Opin. Hematol.* 3:19-26).

ABC Transporters

ATP-binding cassette (ABC) transporters, also called the "traffic ATPases", are a superfamily

WO 00/56891

PCT/US00/07817

of membrane proteins that mediate transport and channel functions in prokaryotes and eukaryotes (Higgins, C.F. (1992) *Annu. Rev. Cell Biol.* 8:67-113). ABC proteins share a similar overall structure and significant sequence homology. All ABC proteins contain a conserved domain of approximately two hundred amino acid residues which includes one or more nucleotide binding domains. Mutations in ABC transporter genes are associated with various disorders, such as hyperbilirubinemia II/Dubin-Johnson syndrome, recessive Stargardt's disease, X-linked adrenoleukodystrophy, multidrug resistance, celiac disease, and cystic fibrosis.

Membrane Proteins Associated with Intercellular Communication

Intercellular communication is essential for the development and survival of multicellular organisms. Cells communicate with one another through the secretion and uptake of protein signaling molecules. The uptake of proteins into the cell is achieved by endocytosis, in which the interaction of signaling molecules with the plasma membrane surface, often via binding to specific receptors, results in the formation of plasma membrane-derived vesicles that enclose and transport the molecules into the cytosol. The secretion of proteins from the cell is achieved by exocytosis, in which molecules inside of the cell are packaged into membrane-bound transport vesicles derived from the *trans* Golgi network. These vesicles fuse with the plasma membrane and release their contents into the surrounding extracellular space. Endocytosis and exocytosis result in the removal and addition of plasma membrane components, and the recycling of these components is essential to maintain the integrity, identity, and functionality of both the plasma membrane and internal membrane-bound compartments.

Lysosomes are the site of degradation of intracellular material during autophagy and of extracellular molecules following endocytosis. Lysosomal enzymes are packaged into vesicles which bud from the *trans*-Golgi network. These vesicles fuse with endosomes to form the mature lysosome in which hydrolytic digestion of endocytosed material occurs. Lysosomes can fuse with autophagosomes to form a unique compartment in which the degradation of organelles and other intracellular components occurs.

Protein sorting by transport vesicles, such as the endosome, has important consequences for a variety of physiological processes including cell surface growth, the biogenesis of distinct intracellular organelles, endocytosis, and the controlled secretion of hormones and neurotransmitters (Rothman, J.E. and Wieland, F.T. (1996) *Science* 272:227-234). In particular, neurodegenerative disorders and other neuronal pathologies are associated with biochemical flaws during endosomal protein sorting or endosomal biogenesis (Mayer R.J. et al. (1996) *Adv. Exp. Med. Biol.* 389:261-269).

Peroxisomes are organelles independent from the secretory pathway. They are the site of many peroxide-generating oxidative reactions in the cell. Peroxisomes are unique among eukaryotic organelles in that their size, number, and enzyme content vary depending upon organism, cell type,

WO 00/56891

PCT/US00/07817

and metabolic needs (Waterham, H.R. and Cregg, J.M. (1997) *BioEssays* 19:57-66). Genetic defects in peroxisome proteins which result in peroxisomal deficiencies have been linked to a number of human pathologies, including Zellweger syndrome, rhizomelic chondrodysplasia punctata, X-linked adrenoleukodystrophy, acyl-CoA oxidase deficiency, bifunctional enzyme deficiency, classical Refsum's disease, DHAP alkyl transferase deficiency, and acatalasemia (Moser, H.W. and Moser, A.B. (1996) *Ann. NY Acad. Sci.* 804:427-441). In addition, Gartner, J. et al. (1991; *Pediatr. Res.* 29:141-146) found a 22 kDa integral membrane protein associated with lower density peroxisome-like subcellular fractions in patients with Zellweger syndrome.

Normal embryonic development and control of germ cell maturation is modulated by a number of secretory proteins which interact with their respective membrane-bound receptors. Cell fate during embryonic development is determined by members of the activin/TGF- β superfamily, cadherins, IGF-2, and other morphogens. In addition, proliferation, maturation, and redifferentiation of germ cell and reproductive tissues are regulated, for example, by IGF-2, inhibins, activins, and follistatins (Petraglia, F. (1997) *Placenta* 18:3-8; Mather, J.P. et al. (1997) *Proc. Soc. Exp. Biol. Med.* 215:209-222).

Endoplasmic Reticulum Membrane Proteins

The normal functioning of the eukaryotic cell requires that all newly synthesized proteins be correctly folded, modified, and delivered to specific intra- and extracellular sites. Newly synthesized membrane and secretory proteins enter a cellular sorting and distribution network during or immediately after synthesis (cotranslationally or posttranslationally) and are routed to specific locations inside and outside of the cell. The initial compartment in this process is the endoplasmic reticulum (ER) where proteins undergo modifications such as glycosylation, disulfide bond formation, and assembly into oligomers. The modified proteins are then transported through a series of membrane-bound compartments which include the various cisternae of the Golgi complex, where further carbohydrate modifications occur. Transport between compartments occurs by means of vesicles that bud and fuse in a manner specific to the type of protein being transported. Once within the secretory pathway, proteins do not have to cross a membrane to reach the cell surface.

Although the majority of proteins processed through the ER are transported out of the organelle, some are retained. The signal for retention in the ER in mammalian cells consists of the tetrapeptide sequence, KDEL, located at the carboxyl terminus of proteins (Munro, S. (1986) *Cell* 46:291-300). Proteins containing this sequence leave the ER but are quickly retrieved from the early Golgi cisternae and returned to the ER, while proteins lacking this signal continue through the secretory pathway.

Disruptions in the cellular secretory pathway have been implicated in several human diseases. In familial hypercholesterolemia the low density lipoprotein receptors remain in the ER,

WO 00/56891

PCT/US00/07817

rather than moving to the cell surface (Pathak, R.K. (1988) J. Cell Biol. 106:1831-1841). Altered transport and processing of the β -amyloid precursor protein (β APP), involves the putative vesicle transport protein presenilin, and may play a role in early-onset Alzheimer's disease (Levy-Lahad, E. et al. (1995) Science 269:973-977). Changes in ER-derived calcium homeostasis have been

5 associated with diseases such as cardiomyopathy, cardiac hypertrophy, myotonic dystrophy, Brody disease, Smith-McCort dysplasia, and diabetes mellitus.

Mitochondrial Membrane Proteins

The mitochondrial electron transport (or respiratory) chain is a series of three enzyme complexes in the mitochondrial membrane that is responsible for the transport of electrons from

10 NADH to oxygen and the coupling of this oxidation to the synthesis of ATP (oxidative phosphorylation). ATP then provides the primary source of energy for driving the many energy-requiring reactions of a cell.

Most of the protein components of the mitochondrial respiratory chain are the products of nuclear encoded genes that are imported into the mitochondria, and the remainder are products of

15 mitochondrial genes. Defects and altered expression of enzymes in the respiratory chain are associated with a variety of disease conditions in man, including, for example, neurodegenerative diseases, myopathies, and cancer.

Lymphocyte and Leukocyte Membrane Proteins

The B-cell response to antigens, which is modulated through receptors, is an essential

20 component of the normal immune system. Mature B cells recognize foreign antigens through B cell receptors (BCR) which are membrane-bound, specific antibodies that bind foreign antigens. The antigen/receptor complex is internalized, and the antigen is proteolytically processed. To generate an efficient response to complex antigens, the BCR, BCR associated proteins, and T cell response are all required. Proteolytic fragments of the antigen are complexed with major histocompatibility

25 complex-II (MHCII) molecules on the surface of the B cells where the complex can be recognized by T cells. In contrast, macrophages and other lymphoid cells present antigens in association with MHCI molecules to T cells. T cells recognize and are activated by the MHCI-antigen complex through interactions with the T cell receptor/CD3 complex, a T cell-surface multimeric protein located in the plasma membrane. T cells activated by antigen presentation secrete a variety of

30 lymphokines that induce B cell maturation and T cell proliferation, and activate macrophages, which kill target cells.

Leukocytes have a fundamental role in the inflammatory and immune response, and include monocytes/macrophages, mast cells, polymorphonucleoleukocytes, natural killer cells, neutrophils, eosinophils, basophils, and myeloid precursors. Leukocyte membrane proteins include members of

35 the CD antigens, N-CAM, I-CAM, human leukocyte antigen (HLA) class I and HLA class II gene

WO 00/56891

PCT/US00/07817

products, immunoglobulins, immunoglobulin receptors, complement, complement receptors, interferons, interferon receptors, interleukin receptors, and chemokine receptors.

Abnormal lymphocyte and leukocyte activity has been associated with acute disorders such as AIDS, immune hypersensitivity, leukemias, leukopenia, systemic lupus, granulomatous disease, and eosinophilia.

Apoptosis-Associated Membrane Proteins

A variety of ligands, receptors, enzymes, tumor suppressors, viral gene products, pharmacological agents, and inorganic ions have important positive or negative roles in regulating and implementing the apoptotic destruction of a cell. Although some specific components of the apoptotic pathway have been identified and characterized, many interactions between the proteins involved are undefined, leaving major aspects of the pathway unknown.

A requirement for calcium in apoptosis was previously suggested by studies showing the involvement of calcium levels in DNA cleavage and Fas-mediated cell death (Hewish, D.R. and L.A. Burgoyne (1973) Biochem. Biophys. Res. Comm. 52:504-510; Vignaux, F. et al. (1995) J. Exp. Med. 181:781-786; Oshimi, Y. and S. Miyazaki (1995) J. Immunol. 154:599-609). Other studies show that intracellular calcium concentrations increase when apoptosis is triggered in thymocytes by either T cell receptor cross-linking or by glucocorticoids, and cell death can be prevented by blocking this increase (McConkey, D.J. et al. (1989) J. Immunol. 143:1801-1806; McConkey, D.J. et al. (1989) Arch. Biochem. Biophys. 269:365-370). Therefore, membrane proteins such as calcium channels are important for the apoptotic response.

The discovery of new human transmembrane proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, immunological, reproductive, smooth muscle, and neurological disorders.

SUMMARY OF THE INVENTION

The invention features purified polypeptides, human transmembrane proteins, referred to collectively as "HTMP" and individually as "HTMP-1," "HTMP-2," "HTMP-3," "HTMP-4," "HTMP-5," "HTMP-6," "HTMP-7," "HTMP-8," "HTMP-9," "HTMP-10," "HTMP-11," "HTMP-12," "HTMP-13," "HTMP-14," "HTMP-15," "HTMP-16," "HTMP-17," "HTMP-18," "HTMP-19," "HTMP-20," "HTMP-21," "HTMP-22," "HTMP-23," "HTMP-24," "HTMP-25," "HTMP-26," "HTMP-27," "HTMP-28," and "HTMP-29." In one aspect, the invention provides an isolated polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, c) a biologically active

WO 00/56891

PCT/US00/07817

fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-29.

5 The invention further provides an isolated polynucleotide encoding a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, or d) an immunogenic
10 fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29. In one alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:30-58.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, b) a naturally occurring amino acid
15 sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention
20 provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, c) a biologically active fragment of an amino acid sequence
25 selected from the group consisting of SEQ ID NO:1-29, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

30 Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, or d) an
35 immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID

WO 00/56891

PCT/US00/07817

NO:1-29.

The invention further provides an isolated polynucleotide comprising a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:30-58, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:30-58, c) a polynucleotide sequence complementary to a), or d) a polynucleotide sequence complementary to b). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:30-58, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:30-58, c) a polynucleotide sequence complementary to a), or d) a polynucleotide sequence complementary to b). The method comprises a) hybridizing the sample with a probe comprising at least 16 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 30 contiguous nucleotides. In another alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a pharmaceutical composition comprising an effective amount of a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, and a pharmaceutically acceptable excipient. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional HTMP, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ

WO 00/56891

PCT/US00/07817

ID NO:1-29. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional HTMP, comprising administering to a patient in need of such treatment the pharmaceutical composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-29. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional HTMP, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:30-58, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding HTMP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of HTMP.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

WO 00/56891

PCT/US00/07817

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding HTMP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze HTMP, along with applicable descriptions, references, and threshold parameters.

5

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

25 DEFINITIONS

"HTMP" refers to the amino acid sequences of substantially purified HTMP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of HTMP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of HTMP either by directly interacting with HTMP or by acting on components of the biological pathway in which HTMP participates.

An "allelic variant" is an alternative form of the gene encoding HTMP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or

35

WO 00/56891

PCT/US00/07817

many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

5 "Altered" nucleic acid sequences encoding HTMP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as HTMP or a polypeptide with at least one functional characteristic of HTMP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding HTMP, and improper or unexpected hybridization to allelic variants,
10 with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding HTMP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent HTMP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the
15 residues, as long as the biological or immunological activity of HTMP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine,
20 isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino
25 acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

30 The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of HTMP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of HTMP either by directly interacting with HTMP or by acting on components of the biological pathway in which HTMP participates.

35 The term "antibody" refers to intact immunoglobulin molecules as well as to fragments

WO 00/56891

PCT/US00/07817

thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind HTMP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic HTMP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" and "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization

WO 00/56891

PCT/US00/07817

between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acid strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding HTMP or fragments of HTMP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of one or more Incyte Clones and, in some cases, one or more public domain ESTs, using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that, when made, least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
	Ala	Gly, Ser
25	Arg	His, Lys
	Asn	Asp, Gln, His
	Asp	Asn, Glu
	Cys	Ala, Ser
	Gln	Asn, Glu, His
30	Glu	Asp, Gln, His
	Gly	Ala
	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
	Leu	Ile, Val
35	Lys	Arg, Gln, Glu
	Met	Leu, Ile
	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
	Thr	Ser, Val
40	Trp	Phe, Tyr
	Tyr	His, Phe, Trp

WO 00/56891

PCT/US00/07817

Val

Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "fragment" is a unique portion of HTMP or the polynucleotide encoding HTMP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:30-58 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:30-58, for example, as distinct from any other sequence in the same genome. A fragment of SEQ ID NO:30-58 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:30-58 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:30-58 and the region of SEQ ID NO:30-58 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-29 is encoded by a fragment of SEQ ID NO:30-58. A fragment

WO 00/56891

PCT/US00/07817

of SEQ ID NO:1-29 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-29. For example, a fragment of SEQ ID NO:1-29 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-29. The precise length of a fragment of SEQ ID NO:1-29 and the region of SEQ ID NO:1-29 to which the fragment
5 corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a
10 target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of
15 reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the
20 substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible
25 way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12c sequence alignment program. This program is part of the LASERGENE software package, a suite of
30 molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent
35 similarity" between aligned polynucleotide sequence pairs.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at

- 5 <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>.
- 10 The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

15 *Reward for match: 1*

Penalty for mismatch: -2

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10

20 *Word Size: 11*

Filter: on

- Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at
- 25 least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

- Nucleic acid sequences that do not show a high degree of identity may nevertheless encode
- 30 similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

- The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a
- 35 standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some

WO 00/56891

PCT/US00/07817

alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the hydrophobicity and acidity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 3

Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of identity.

WO 00/56891

PCT/US00/07817

Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Generally, such wash temperatures are selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization are well known and can be found in Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide

WO 00/56891

PCT/US00/07817

sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of HTMP which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of HTMP which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" and "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

The term "modulate" refers to a change in the activity of HTMP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of HTMP.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Probe" refers to nucleic acid sequences encoding HTMP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes.

"Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target

polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel et al., 1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization

WO 00/56891

PCT/US00/07817

technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding HTMP, or fragments thereof, or HTMP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by

WO 00/56891

PCT/US00/07817

different amino acids or nucleotides, respectively.

“Substrate” refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

“Transformation” describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term “transformed” cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A “transgenic organism,” as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, and plants and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

A “variant” of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the “BLAST 2 Sequences” tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an “allelic” (as defined above), “splice,” “species,” or “polymorphic” variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of

WO 00/56891

PCT/US00/07817

polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

10 A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human transmembrane proteins (HTMP), the polynucleotides encoding HTMP, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, immunological, reproductive, smooth muscle, and neurological disorders.

20 Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding HTMP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each HTMP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The Incyte clones in column 5 were used to assemble the consensus nucleotide sequence of each HTMP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: 30 column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows the identity of each polypeptide and homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each 35

WO 00/56891

PCT/US00/07817

polypeptide through sequence homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding HTMP. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:30-58 and to distinguish between SEQ ID NO:30-58 and related polynucleotide sequences. The polypeptides encoded by the specified fragments of SEQ ID NO:30-58 are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express HTMP as a fraction of total tissues expressing HTMP. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing HTMP as a fraction of total tissues expressing HTMP. Column 5 lists the vectors used to subclone each cDNA library. Of particular note is the expression of SEQ ID NO:41 in 21 libraries, of which 15 (71%) are associated with nervous tissue.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding HTMP were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

SEQ ID NO:45 maps to chromosome 3 within the interval from 49.50 to 55.40 centiMorgans. This interval also contains genes associated with disorders of cell proliferation. SEQ ID NO:47 maps to chromosome 7 within the interval from 74.30 to 76.40 centiMorgans. This interval also contains an EST associated with cell proliferation. SEQ ID NO:50 maps to chromosome 2 within the interval from 111.5 to 115.3 centiMorgans. This interval also contains genes associated with immune response. SEQ ID NO:51 maps to chromosome 11 within the interval from 84.2 to 87.1 centiMorgans. This interval also contains a gene associated with immune response. SEQ ID NO:53 maps to chromosome 13 within the interval from 77.10 to 86.90 centiMorgans. This interval also contains genes associated with immune response. SEQ ID NO:55 maps to chromosome 1 within the interval from 74.80 to 78.30 centiMorgans. This interval also contains a gene associated with immune response. SEQ ID NO:58 maps to chromosome 15 within the interval from the p-terminus to 25.30 centiMorgans. This interval also contains a gene associated with cell proliferation.

The invention also encompasses HTMP variants. A preferred HTMP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the HTMP amino acid sequence, and which contains at least one functional or structural characteristic of HTMP.

The invention also encompasses polynucleotides which encode HTMP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:30-58, which encodes HTMP. The polynucleotide

WO 00/56891

PCT/US00/07817

sequences of SEQ ID NO:30-58, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding HTMP. In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding HTMP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:30-58 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:30-58. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of HTMP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding HTMP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring HTMP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode HTMP and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring HTMP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding HTMP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding HTMP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode HTMP and HTMP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding HTMP or any fragment thereof.

WO 00/56891

PCT/US00/07817

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:30-58 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.* 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Perkin-Elmer). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Perkin-Elmer), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding HTMP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) *PCR Methods Applic.* 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) *Nucleic Acids Res.* 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) *PCR Methods Applic.* 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) *Nucleic Acids Res.* 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries

WO 00/56891

PCT/US00/07817

(Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in
5 length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T)
10 library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-
15 specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments
20 which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode HTMP may be cloned in recombinant DNA molecules that direct expression of HTMP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a
25 functionally equivalent amino acid sequence may be produced and used to express HTMP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter HTMP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic
30 oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number
35 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat.

Biotechnol. 17:259-264; and Crameri, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of HTMP, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then
5 subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are
10 optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding HTMP may be synthesized, in whole or in part,
15 using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively, HTMP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the
20 ABI 431A peptide synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of HTMP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.)
25 The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active HTMP, the nucleotide sequences encoding HTMP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains
30 the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding HTMP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding HTMP. Such signals
35 include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where

WO 00/56891

PCT/US00/07817

sequences encoding HTMP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector. no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding HTMP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding HTMP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding HTMP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding HTMP can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding HTMP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of HTMP are needed, e.g. for the production of antibodies, vectors which direct high level expression of HTMP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of HTMP. A number of vectors

WO 00/56891

PCT/US00/07817

containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 5 1995, supra; Bitter, G.A. et al. (1987) *Methods Enzymol.* 153:516-544; and Scorer, C.A. et al. (1994) *Bio/Technology* 12:181-184.)

Plant systems may also be used for expression of HTMP. Transcription of sequences encoding HTMP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 10 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology 15 (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding HTMP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain 20 infective virus which expresses HTMP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) *Proc. Natl. Acad. Sci. USA* 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of 25 DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) *Nat. Genet.* 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression 30 of HTMP in cell lines is preferred. For example, sequences encoding HTMP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance 35 to a selective agent, and its presence allows growth and recovery of cells which successfully express

the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* and *apr*^r cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding HTMP is inserted within a marker gene sequence, transformed cells containing sequences encoding HTMP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding HTMP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding HTMP and that express HTMP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of HTMP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on HTMP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See,

e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press. St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

5 A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding HTMP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding HTMP, or any fragments thereof, may be cloned into a vector
10 for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for
15 ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding HTMP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence
20 and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode HTMP may be designed to contain signal sequences which direct secretion of HTMP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of
25 the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the
30 American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding HTMP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric HTMP protein
35 containing a heterologous moiety that can be recognized by a commercially available antibody may

WO 00/56891

PCT/US00/07817

facilitate the screening of peptide libraries for inhibitors of HTMP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the HTMP encoding sequence and the heterologous protein sequence, so that HTMP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, *supra*, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled HTMP may be achieved *in vitro* using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ³⁵S-methionine.

Fragments of HTMP may be produced not only by recombinant means, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, *supra*, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A peptide synthesizer (Perkin-Elmer). Various fragments of HTMP may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of HTMP and human transmembrane proteins. In addition, the expression of HTMP is closely associated with cell proliferation and the immune response, and with cardiovascular, gastrointestinal, reproductive, and neurological tissues. Therefore, HTMP appears to play a role in cell proliferative, immunological, reproductive, smooth muscle, and neurological disorders. In the treatment of disorders associated with increased HTMP expression or activity, it is desirable to decrease the expression or activity of HTMP. In the treatment of disorders associated with decreased HTMP expression or activity, it is desirable to increase the expression or activity of HTMP.

Therefore, in one embodiment, HTMP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or

WO 00/56891

PCT/US00/07817

activity of HTMP. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immunological disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a reproductive disorder such as a disorder of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, a disruption of the estrous cycle, a disruption of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, an endometrial or ovarian tumor, a uterine fibroid, autoimmune disorders, an ectopic pregnancy, and teratogenesis, cancer of the breast, fibrocystic breast disease, and galactorrhea, a disruption of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; a smooth muscle disorder such as angina, anaphylactic shock, arrhythmias, asthma, cardiovascular shock, Cushing's syndrome, hypertension, hypoglycemia, myocardial infarction, migraine, and pheochromocytoma, and myopathies including cardiomyopathy, encephalopathy, epilepsy, Kearns-Sayre syndrome, lactic acidosis, myoclonic disorder, and ophthalmoplegia; and a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis

WO 00/56891

PCT/US00/07817

pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal
 5 familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system
 10 disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy, corticobasal degeneration, and familial frontotemporal dementia.

15 In another embodiment, a vector capable of expressing HTMP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTMP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified HTMP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat
 20 or prevent a disorder associated with decreased expression or activity of HTMP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of HTMP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTMP including, but not limited to, those listed above.

25 In a further embodiment, an antagonist of HTMP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HTMP. Examples of such disorders include, but are not limited to, those cell proliferative, immunological, reproductive, smooth muscle, and neurological disorders described above. In one aspect, an antibody which specifically binds HTMP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism
 30 for bringing a pharmaceutical agent to cells or tissues which express HTMP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding HTMP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HTMP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary
 35 sequences, or vectors of the invention may be administered in combination with other appropriate

WO 00/56891

PCT/US00/07817

therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of HTMP may be produced using methods which are generally known in the art. In particular, purified HTMP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind HTMP. Antibodies to HTMP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies. Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with HTMP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to HTMP have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of HTMP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to HTMP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc.

WO 00/56891

PCT/US00/07817

Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce HTMP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be
5 generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA
10 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for HTMP may also be generated. For example, such fragments include, but are not limited to, F(ab')₂ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and
15 easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such
20 immunoassays typically involve the measurement of complex formation between HTMP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering HTMP epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay
25 techniques may be used to assess the affinity of antibodies for HTMP. Affinity is expressed as an association constant, K_a , which is defined as the molar concentration of HTMP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple HTMP epitopes, represents the average affinity, or avidity, of the antibodies for
30 HTMP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular HTMP epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the HTMP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar
35 procedures which ultimately require dissociation of HTMP, preferably in active form, from the

Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in
5 Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme
10 molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding HTMP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA,
15 GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

20 Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding HTMP. Such DNA sequences may be incorporated into a wide variety of vectors
25 with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3'
30 ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous
35 endonucleases.

WO 00/56891

PCT/US00/07817

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of HTMP, antibodies to HTMP, and mimetics, agonists, antagonists, or inhibitors of HTMP. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose,

WO 00/56891

PCT/US00/07817

hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

5 Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

10 Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or
15 liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or
20 dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of
25 highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating,
30 dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acids. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder which may contain any
35 or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a

WO 00/56891

PCT/US00/07817

pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of HTMP, such labeling would include amount, frequency, and method of administration.

5 Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, or pigs.

10 An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example HTMP or fragments thereof, antibodies of HTMP, and agonists, antagonists or inhibitors of HTMP, 15 which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions 20 which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

25 The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and 30 response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and 35 methods of delivery is provided in the literature and generally available to practitioners in the art.

WO 00/56891

PCT/US00/07817

Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

5 In another embodiment, antibodies which specifically bind HTMP may be used for the diagnosis of disorders characterized by expression of HTMP, or in assays to monitor patients being treated with HTMP or agonists, antagonists, or inhibitors of HTMP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for HTMP include methods which utilize the antibody and a label to detect HTMP in human body
10 fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring HTMP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of HTMP expression. Normal
15 or standard values for HTMP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to HTMP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of HTMP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values.
20 Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding HTMP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of HTMP may be correlated
25 with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of HTMP, and to monitor regulation of HTMP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding HTMP or closely related molecules may be used to identify nucleic acid sequences which encode HTMP. The specificity of the probe, whether it is
30 made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding HTMP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50%
35 sequence identity to any of the HTMP encoding sequences. The hybridization probes of the subject

WO 00/56891

PCT/US00/07817

invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:30-58 or from genomic sequences including promoters, enhancers, and introns of the HTMP gene.

Means for producing specific hybridization probes for DNAs encoding HTMP include the cloning of polynucleotide sequences encoding HTMP or HTMP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding HTMP may be used for the diagnosis of disorders associated with expression of HTMP. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immunological disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a reproductive disorder such as a disorder of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, a disruption of the estrous cycle, a disruption of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, an endometrial or ovarian tumor, a uterine fibroid, autoimmune disorders, an ectopic pregnancy, and teratogenesis, cancer of

WO 00/56891

PCT/US00/07817

the breast, fibrocystic breast disease, and galactorrhea, a disruption of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; a smooth muscle disorder such as angina, anaphylactic shock, arrhythmias, asthma, cardiovascular shock, Cushing's syndrome, hypertension, hypoglycemia, myocardial infarction, migraine, and pheochromocytoma, and myopathies including cardiomyopathy, encephalopathy, epilepsy, Kearns-Sayre syndrome, lactic acidosis, myoclonic disorder, and ophthalmoplegia; and a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy, corticobasal degeneration, and familial frontotemporal dementia.

The polynucleotide sequences encoding HTMP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered HTMP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding HTMP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding HTMP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding HTMP in the

WO 00/56891

PCT/US00/07817

sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of HTMP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding HTMP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding HTMP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding HTMP, or a fragment of a polynucleotide complementary to the polynucleotide encoding HTMP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of HTMP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer of interest is

presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray
5 can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g.,
10 Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding HTMP may be used
15 to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price,
20 C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the
25 location of the gene encoding HTMP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as
30 linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other
35 gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic

WO 00/56891

PCT/US00/07817

linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, HTMP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between HTMP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with HTMP, or fragments thereof, and washed. Bound HTMP is then detected by methods well known in the art. Purified HTMP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding HTMP specifically compete with a test compound for binding HTMP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with HTMP.

In additional embodiments, the nucleotide sequences which encode HTMP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications and publications, mentioned above and below, in particular U. S. Ser. No. 60/125,537 and U. S. Ser. No. 60/139,565, are hereby expressly incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A⁺) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, *supra*, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), pcDNA2.1 plasmid (Invitrogen, Carlsbad CA), or pINCY plasmid (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 α , DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by *in vivo* excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or

WO 00/56891

PCT/US00/07817

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:30-58. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\% \text{ sequence identity} \times \% \text{ maximum BLAST score}}{100}$$

30

100

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

35

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding HTMP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

10 V. Chromosomal Mapping of HTMP Encoding Polynucleotides

The cDNA sequences which were used to assemble SEQ ID NO:30-58 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:30-58 were assembled into clusters of contiguous and overlapping sequences using
15 assembly algorithms such as Phrap (Table 5). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO., to that map location.

20 The genetic map locations of SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, and SEQ ID NO:58 are described in The Invention as ranges, or intervals, of human chromosomes. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM
25 is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Diseases associated with the public and Incyte sequences located within the indicated intervals are also reported in the Invention where applicable.

30 VI. Extension of HTMP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:30-58 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using
35 OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30

nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one
5 extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$, and β -mercaptoethanol. Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme
10 (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times;
15 Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II
20 (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μ l to 10 μ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates,
25 digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham
30 Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase
35 (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following

WO 00/56891

PCT/US00/07817

parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:30-58 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VII. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:30-58 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μ Ci of [γ -³²P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10⁷ counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

VIII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, *supra*.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and

patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

IX. Complementary Polynucleotides

Sequences complementary to the HTMP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring HTMP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of HTMP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the HTMP-encoding transcript.

X. Expression of HTMP

Expression and purification of HTMP is achieved using bacterial or virus-based expression systems. For expression of HTMP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express HTMP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of HTMP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding HTMP by either homologous recombination or bacterial-mediated

WO 00/56891

PCT/US00/07817

transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect *Spodoptera frugiperda* (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, HTMP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from *Schistosoma japonicum*, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from HTMP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, *supra*, ch. 10 and 16). Purified HTMP obtained by these methods can be used directly in the following activity assay.

XI. Demonstration of HTMP Activity

An assay for HTMP activity measures the expression of HTMP on the cell surface. cDNA encoding HTMP is transfected into an appropriate mammalian cell line. Cell surface proteins are labeled with biotin as described (de la Fuente, M. A. et al. (1997) Blood 90:2398-2405). Immunoprecipitations are performed using HTMP-specific antibodies, and immunoprecipitated samples are analyzed using SDS-PAGE and immunoblotting techniques. The ratio of labeled immunoprecipitant to unlabeled immunoprecipitant is proportional to the amount of HTMP expressed on the cell surface.

An alternative assay for HTMP activity is based on a prototypical assay for ligand/receptor-mediated modulation of cell proliferation. This assay measures the amount of newly synthesized DNA in Swiss mouse 3T3 cells expressing HTMP. An appropriate mammalian expression vector containing cDNA encoding HTMP is added to quiescent 3T3 cultured cells using transfection methods well known in the art. The transfected cells are incubated in the presence of [³H]thymidine and varying amounts of HTMP ligand. Incorporation of [³H]thymidine into acid-precipitable DNA is measured over an appropriate time interval using a tritium radioisotope counter, and the amount incorporated is directly proportional to the amount of newly synthesized DNA. A linear dose-response curve over at least a hundred-fold HTMP ligand concentration range is indicative of receptor

WO 00/56891

PCT/US00/07817

activity. One unit of activity per milliliter is defined as the concentration of HMTMP producing a 50% response level, where 100% represents maximal incorporation of [³H]thymidine into acid-precipitable DNA (McKay, I. and Leigh, I., eds. (1993) Growth Factors: A Practical Approach, Oxford University Press, New York, NY, p. 73).

- 5 Alternatively, an assay for HMTMP activity measures the effect of HMTMP expression on the regulation of cell growth. To demonstrate that increased levels of HMTMP expression correlates with decreased cell motility and increased cell proliferation, expression vectors encoding HMTMP are electroporated into highly motile cell lines, such as U-937 (ATCC CRL 1593), HEL 92.1.7 (ATCC TIB 180) and MAC10, and the motility of the electroporated and control cells are compared.
- 10 Methods for the design and construction of an expression vector capable of expressing HMTMP in the desired mammalian cell line(s) chosen are well known to the art. Assays for examining the motility of cells in culture are known to the art (cf Miyake, M. et al. (1991) J. Exp. Med. 174:1347-1354 and Ikeyama, S. et al. (1993) J. Exp. Med. 177:1231-1237). Increasing the level of HMTMP in highly motile cell lines by transfection with an HMTMP expression vector inhibits or reduces the motility of
- 15 these cell lines, and the amount of this inhibition is proportional to the activity of HMTMP in the assay.

XII. Functional Assays

- HTMP function is assessed by expressing the sequences encoding HTMP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice
- 20 include pCMV SPORT plasmid (Life Technologies) and pCR3.1 plasmid (Invitrogen), both of which contain the cytomegalovirus promoter. 5-10 μ g of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 μ g of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish
 - 25 transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of
 - 30 fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with
 - 35 specific antibodies; and alterations in plasma membrane composition as measured by the binding of

WO 00/56891

PCT/US00/07817

fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of HTMP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding HTMP and either CD64 or CD64-GFP.

- 5 CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding HTMP and other genes of interest can be analyzed by
10 northern analysis or microarray techniques.

XIII. Production of HTMP Specific Antibodies

HTMP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

- 15 Alternatively, the HTMP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

- 20 Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for anti-peptide and anti-
25 HTMP activity by, for example, binding the peptide or HTMP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIV. Purification of Naturally Occurring HTMP Using Specific Antibodies

Naturally occurring or recombinant HTMP is substantially purified by immunoaffinity chromatography using antibodies specific for HTMP. An immunoaffinity column is constructed by
30 covalently coupling anti-HTMP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

- Media containing HTMP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of HTMP (e.g., high ionic strength
35 buffers in the presence of detergent). The column is eluted under conditions that disrupt

antibody/HTMP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and HTMP is collected.

XV. Identification of Molecules Which Interact with HTMP

HTMP, or biologically active fragments thereof, are labeled with ¹²⁵I Bolton-Hunter reagent.
5 (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled HTMP, washed, and any wells with labeled HTMP complex are assayed. Data obtained using different concentrations of HTMP are used to calculate values for the number, affinity, and association of HTMP with the candidate molecules.

10 Alternatively, molecules interacting with HTMP are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989, Nature 340:245-246), or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

Various modifications and variations of the described methods and systems of the invention
15 will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the
20 scope of the following claims.

Table 1

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	30	1316927	BLADTUT02	452732R1 (TLVNOT02), 1316927H1 (BLADTUT02), 1333144F6 (PANCNOT07), 1428681F1 (SINTBST01), 2671590F6 (ESOGTUT02)
2	31	1354891	LUNGNOT09	1354891H1 (LUNGNOT09), 2847485F6 (DRGLNOT01), 3290718F6 (BONRFET01)
3	32	1415487	BRAINOT12	667705R6 (SCORNOT01), 1415487H1 (BRAINOT12), 2350869H1 (COLSUCT01), 2380229F6 (ISLTNOT01), 2764913H1 (BRSTNOT12), 2805580H1 (BLADTUT08), 2921276H1 (SININOT04), 2997732H1 (OVARUTUT07), 3110058F6 (BRSTTUT15), 3689409F6 (HEAANOT01), SBAA02719F1, SBAA05351F1, SBAA01910F1, SBAA01637F1
4	33	1693184	COLNNOT23	723435R1 (SYNOOAT01), 1227091T6 (COLNNOT01), 1260955R1 (SYNORAT05) 1801610H1 (COLNNOT27), 3221682H1 (COLNNON03), 3272150H1 (BRAINOT20)
5	34	1695049	COLNNOT23	941876H1 (ADRENOT03), 1695049F6 and 1695049H1 (COLNNOT23), 1864817F6 (PROSNOT19), 1867837H1 (SKINBIT01), 2659996F6 (LUNGNOT09), 3561726F6 (SKINNOT05), 3647351H1 (ENDINOT01)
6	35	1802448	COLNNOT27	1510235F1 (LUNGNOT14), 15623316F1 (SPLNNOT04), 1671093F6 (BMARNOT03), 1694276F6 (COLNNOT23), 1802448H1 and 1802448T6 (COLNNOT27), 2149391F6 (BRAINOT09), 2705476F6 (PONSATZT01), 2804539F6 (BLADTUT08), 4792839H1 (EPIBUNT01), 5397728H1 (LIVRTUT13)
7	36	2057214	BEPINOT01	1271518F6 (TESTTUT02), 1365446R1 and 1365446T1 (SCORNON02), 1967159R6 (BRSTNOT04), 2057214H1 (BEPINOT01), 2173927F6 and 2173927T6 (ENDCNOT03), 2556249F6 (THYMNOT03), SBDA02536F1
8	37	2448177	THPINOT03	1718148F6 (UCMCNOT02), 2448177H1 (THPINOT03), 2520263H1 (BRAITUT21), SCBA02093V1, SCBA01393V1, SCBA01143V1
9	38	2741701	BRSTTUT14	1648954F6 (PROSTUT09), 3418901H1 (UCMCNOT04), 2741701F6 (BRSTTUT14), 3247835H1 (SEMVNOT03), 3869680F6 (BMARNOT03), 1809373F6 (PROSTUT12), 992617R6 (COLNNOT11), SBFA01145F1
10	39	3487228	EPIGNOT01	3408591F6 (PROSTU08), 3487228F6 (EPIGNOT01), 3487228H1 (EPIGNOT01)
11	40	3671426	KIDNTUT16	3671426H1 and 3671426T6 (KIDNTUT16), SASB01034F1, SASB01530F1, SASB00221F1, SASB01242F1

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
12	41	4020882	BRAXNOT02	2413217R6 (BSTMN02), 4020882H1 (BRAXNOT02), SBXA03463D1, SBXA01344D1, SBXA02823D1, SBXA03612D1, SBXA01807D1
13	42	4069777	KIDNNOT26	4069777F6 and 4069777H1 (KIDNNOT26), 4560189F6 (KERATXT01), 4576433H1 (LUNLTUT02), SBGA05674F1
14	43	5309830	MONOTXT02	1274762F6 (TESTTUT02), 1348268T6 (PROSN01), 2110201X13F1 and 2110201X17F1 (BRAITUT03), 5309830H1 (MONOTXT02), SAGA02951F1, SAGA02413F1
15	44	306263	HEARNOT01	04615V1 (HMCINOT01), 167880R6 (LIVRN0T01), 306263H1 (HEARNOT01), 306263R6 (HEARNOT01), 307430T6 (HEARNOT01), 1391023F6 (EOSINOT01), 2074431H1 (ISLTN0T01), 4938418H1 (EPIMN04), 5513730H1 (BRADDIR01), SCHA04615V1
16	45	483751	HNT2RAT01	037180H1 (HUVENOB01), 143478R1 (TLYMNOR01), 378814H1 (NEUTFM01), 483751H1 (HNT2RAT01), 483751R6 (HNT2RAT01), 776822R1 (COLNNOT05), 962802R2 (BRSTTUT03), 1353469F1 (LATRTUT02)
17	46	727332	SYNOOAT01	727332H1 (SYNOOAT01), 1484843T1 (CORPNOT02), 2349284T6 (COLSUCT01), 2705135H1 (PONSAT01), 4172701F6 (SINTNOT21), SBYA04629U1, SBYA05701U1, SBYA06282U1, SBYA05724U1
18	47	778800	MYOMNOT01	071616F1 (PLACNOB01), 438858T6 (THYRN0T01), 778800F1 (MYOMNOT01), 778800H1 (MYOMNOT01), 778935R1 (MYOMNOT01), 2638524F6 (BONTN0T01), 4989972H1 (LIVRTUT11), 4996486H1 (MYEPTXT02), 5609965H1 (MONOTXS05)
19	48	1396995	BRAITUT08	1396995H1 (BRAITUT08), 1396995X318U1 (BRAITUT08), 1400161T6 (BRAITUT08), 3519719R6 (LUNGNON03), 3519719T6 (LUNGNON03)
20	49	1597730	BRAINOT14	1597730H1 (BRAINOT14), 2756450T6 (THP1AZS08), 2898729T6 (THYMNON02)
21	50	1629304	COLNPOT01	898259H1 (BRSTNOT05), 1000577R6 (BRSTNOT03), 1629304F6 (COLNPOT01), 1629304H1 (COLNPOT01), 1807094F6 (SINTNOT13), 2628947H1 (PROSTUT12), 3142908H1 (HNT2AZS07), 3217195H1 (TESTNOT07)

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
22	51	1989585	CORPNOT02	470971T6 (MMLR1DT01), 871981R7 (LUNGAST01), 1602687F6 (BLADNOT03), 1989585H1 (CORPNOT02), 1989585T6 (CORPNOT02), 2250984X312D1 (OVARUT01), 2293025R6 (BRAINOT01), 4143919H1 (BRSTTMT01), 4855964H1 (BRSTTUT22)
23	52	2134729	ENDCNOT01	1734329F6 (COLNNOT22), 2134729H1 (ENDCNOT01), 2857991H1 (CONNNOT02), 2884112H1 (SINJNOT02), 2970301F6 (HEAONOT02), 3437438F6 (PENCNOT05), 4061613H1 (BRAINOT21), 4239422H1 (SYNWDIT01), 4896767H1 (LIVRTUT12)
24	53	2299506	BRSTNOT05	1226895T1 (COLNNOT01), 1469923F1 (PANCTUT02), 2299506H1 (BRSTNOT05), 2299506R6 (BRSTNOT05), 2748977F6 (LUNGUTUT11)
25	54	2506558	CONUTUT01	838594H1 (PROSTUT05), 1851144F6 (LUNGFET03), 2506558F6 (CONUTUT01), 2506558H1 (CONUTUT01), 3046030H1 (HEAANOT01), 3475919T6 (LUNGNOT27), 4776339H1 (BRAONOT01)
26	55	2546025	UTRSNOT11	000451H1 (U937NOT01), 820914T1 (KERANOT02), 1441359F1 (THYRNOT03), 1441359R1 (THYRNOT03), 2546025H1 (UTRSNOT11), 3602668H1 (DRGTNOT01)
27	56	3145660	ENDCNOT04	3069110F6 (UTRSNOR01), 3145660F6 (ENDCNOT04), 3145660H1 (ENDCNOT04)
28	57	4901066	OVARDIT01	1752794F6 (LIVRTUT01), 3221661R6 (COLNNOT03), 4901066H1 (OVARDIT01), SEQA03652D1, SEQA04510D1
29	58	5031174	BRSTTMT02	033456F1 (THP1NOB01), 082616R6 (HUVESB01), 1442589T6 (THYRNOT03), 1506778F6 (BRAITUT07), 1643902F6 (HEARFET01), 1901162H1 (BLADTUT06), 2526581H1 (BRAITUT21), 5031174H1 (BRSTTMT02), 5470948H1 (MCLRUNT01)

Table 2

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Identification/ Homologous Sequences	Analytical Methods and Databases
1	417	T19 T48 S53 T248 T402 T52 T142 S196 T238 T261 T300 T329 S395	N9 N17 N190 N236 N239	V163-L178 (aldo/keto reductase) L374-A392 (transmembrane)	membrane glycoprotein g2114323	MOTIFS BLAST HMM
2	316	S70 S108 T123 S73	N139 N143	M1-P39 (signal peptide)	DP2 (transcription factor) g1698896	MOTIFS BLAST SPSCAN
3	273	S76 T63 T152 S239 S16 T17 S101 S137 S156 T193	N99	I2-C28 (transmembrane) M1-G38 (signal peptide)	Voltage-gated Na ⁺ channel subtype II g3075512	MOTIFS BLAST HMM SPSCAN
4	222	S9 T48 T215		I62-I79, S155-C177 (transmembrane) M1-A35 (signal peptide)	CAC-1 (beta-casein-like protein) g6482350	MOTIFS HMM SPSCAN BLAST
5	329	T285 T325	N51 N171 N269	Y19-W41, W65-G84, L92-V116, N234-Q257 (transmembrane) K18-I263 (tetraspan) Y19-A42, G60-F115, V237-I263 (tetraspan) C15-A33, L66-F104, A149-G160, N234-I263 (tetraspan) L58-L113 (tetraspan)	Tetraspan protein g3152703	MOTIFS BLAST HMM PFAM PRINTS BLOCKS PROFILESCAN

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Identification/ Homologous Sequences	Analytical Methods and Databases
6	351	T335 S340 S54 S93 T203 T288 S344	N284	C161-W183 (transmembrane)	Similar to vanadate resistance protein transmembranous domains g3875131	MOTIFS BLAST HMM
7	489	S291 S10 T51 T52 T135 S185 S244 T416 S143 T224 T252 T279 S379 S483	N105 N121	L263-L284, L399-L420 (Leucine zipper) C23-L41, L65-L82, G111- F134, Y152-W170, L306- L324, F345-M364, W429- F455 (transmembrane)	Transmembrane protein	MOTIFS HMM
8	291	T212 T280 T178 S283	N10	A37-F57, I215-L232, W255- F273 (transmembrane) M1-P55 (signal peptide)	Seven transmembrane protein g1314162	MOTIFS HMM SPSCAN BLAST
9	172	T88		M64-F82 (transmembrane) M1-C42 (signal peptide)	Transmembrane protein	MOTIFS HMM SPSCAN
10	155	T92 S94 S114 S136		V19-W42, L46-E65 (aromatic amino acid permease) G41-F57 (transmembrane)	Transmembrane protein	MOTIFS PRINTS HMM
11	578	T133 S516 S59 S263 T273 T38 T75 T169 T273 S461 S518 Y387		V185-W204, M327-C350 (transmembrane) M1-A18 (signal peptide)	Transmembrane protein g1070391	MOTIFS BLAST HMM SPSCAN

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Identification/ Homologous Sequences	Analytical Methods and Databases
12	313	S65 S101 T114 S137 S165 T167 T258 S289 S50 S64 T207 S222 S223 S254 T277		L182-F201 (transmembrane)	Transmembrane protein	MOTIFS HMM
13	205	S108 S147 T158 T37 T92 T169 S173 T197		M1-S18 (signal peptide) M71-A90 (transmembrane)	Transmembrane protein	MOTIFS SPSCAN HMM
14	371	S78 S165 T245 S354 S24 T290 S297	N110 N269	M1-N21 (signal peptide)	Transmembrane protein	MOTIFS SPSCAN
15	374	S10 S57 T59 T74 S312 S130 T193 S322 Y33	N320	L49-L70 (Leucine zipper gene regulatory pattern) L345-Y367 (transmembrane motif) Q222-L333 (Calponin family repeat motif)	g499184 neuronal protein	MOTIFS HMMER BLAST-DMO BLIMPS-BLOCKS BLAST-GenBank
16	183	T10 T11 S126 T131 T172 T99 T171	N170	G67-Y89, S104-T127, I138- Y157 (transmembrane motifs)		MOTIFS HMMER
17	190	T14 S20 S70 S59 S102 Y66	N13 N62 N131	S188-I190 (Microbodies C- terminal targeting signal) L169-F187 (transmembrane motif) R31-W154 (transmembrane protein)		MOTIFS HMMER BLAST-PRODOM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Identification/ Homologous Sequences	Analytical Methods and Databases
18	361	S120 S30 S315	N319	L36-L57 (Leucine zipper gene regulatory pattern) L28-V48 (transmembrane motif)		MOTIFS HMMER
19	97	T25	N20	S63-F80 (transmembrane motif)		MOTIFS HMMER
20	232	S49 S68 T103 S104 T39 T92 S181 S216 Y191	N37	L20-F35 (Crystallins beta and gamma signature) M50-Y76, Y131-L158 (transmembrane motifs)	Protein tyrosine phosphatase-like protein PTPLB g6851256	MOTIFS HMMER BLAST
21	271	S39 T59	N37 N41 N111	M1-T21 (Signal peptide) R178-F196, I218-T244 (transmembrane motifs)	TM6P1 (6 transmembrane domain protein) g6013381	MOTIFS HMMER BLAST
22	267	S16 S54 T83 S198 Y63	N24	L121-Y136, Q146-W166, T177-F195 (transmembrane motifs) P3-Y168, Y119-V258 (transmembrane protein)		MOTIFS HMMER BLAST-PRODOM BLAST-DOMO
23	406	S4 T99 S113 S125 S136 S365 S59 T87 S94 Y281	N31 N112	I288-Y313 (transmembrane motif) P9-N406 (transmembrane protein)	g2358019 Homo sapiens T-cell receptor alpha delta locus	MOTIFS HMMER BLAST-PRODOM BLAST-GenBank

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Identification/ Homologous Sequences	Analytical Methods and Databases
24	318	S56 S254 L315 S66 T172 S193 Y180	N313	F8-G26 (transmembrane motif)		MOTIFS HMMER
25	326	S195 T321 S21 S62 S69 S90 S186 T282 T305 S75 S94 T213 S228 S307 Y135 Y264	N290 N294	L231-I250 (transmembrane motif)		MOTIFS HMMER
26	247	S27 S235 S12 T26 S33 S70 S93 S179		L214-S234 (transmembrane motif)	g4128007 hyperion gene	MOTIFS HMMER BLAST-GenBank
27	278	S259		G276-F278 (Microbodies C-terminal targeting signal) F137-L155, L176-G195, I262-F278 (transmembrane motifs)		MOTIFS HMMER
28	320	T280 S285 S86 T96 T131 Y156	N84 N109 N121	L197-L218 (Leucine zipper gene regulatory pattern) M1-A35 (Signal peptide) P23-I45, L208-I227, L254-Y272 (transmembrane motifs)		MOTIFS HMMER SPSCAN
29	360	S43 T138 S143 S312 S351	N244 N323 N349 N356	F10-I29, F151-G170, I280-F299 (transmembrane motifs)		MOTIFS HMMER

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
30	148-192	Gastrointestinal (0.280) Reproductive (0.240) Nervous (0.180)	Cell proliferation (0.580) Immune response (0.340)	pINCY
31	217-261	Nervous (0.250) Gastrointestinal (0.200) Reproductive (0.200)	Cell proliferation (0.700) Immune response (0.300)	pINCY
32	597-641	Nervous (0.280) Reproductive (0.220) Gastrointestinal (0.140)	Cell proliferation (0.660) Immune response (0.360)	pINCY
33	219-263	Gastrointestinal (0.354) Reproductive (0.271) Nervous (0.083)	Cell proliferation (0.605) Immune response (0.375)	pINCY
34	923-967	Gastrointestinal (0.182) Nervous (0.182) Cardiovascular (0.159)	Cell proliferation (0.636) Immune response (0.409)	pINCY
35	273-317	Gastrointestinal (0.231) Reproductive (0.212) Musculoskeletal (0.135)	Cell proliferation (0.731) Immune response (0.288)	pINCY
36	435-479	Reproductive (0.222) Gastrointestinal (0.208) Cardiovascular (0.125) Nervous (0.125)	Cell proliferation (0.653) Immune response (0.361)	PSPORT1
37	381-425	Reproductive (0.312) Nervous (0.281) Hematopoietic/Immune (0.188)	Cell proliferation (0.657) Immune response (0.375)	pINCY
38	165-209	Gastrointestinal (0.231) Nervous (0.154) Reproductive (0.154)	Cell proliferation (0.731) Immune response (0.231)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
39	137-181	Nervous (0.333) Reproductive (0.333) Cardiovascular (0.333)	Immune response (0.333) Cell proliferation (0.667)	pINCY
40	456-500	Reproductive (0.324) Nervous (0.206) Hematopoietic/Immune (0.118)	Cell proliferation (0.706) Immune response (0.353)	pINCY
41	354-398	Nervous (0.714) Developmental (0.095) Dermatologic (0.048)	Cell proliferation (0.619) Immune response (0.381)	pINCY
42	273-317	Urologic (0.333) Cardiovascular (0.167) Dermatologic (0.167) Nervous (0.167) Reproductive (0.167)	Cell proliferation (0.834) Neurological (0.167)	pINCY
43	149-193	Reproductive (0.417) Urologic (0.167) Cardiovascular (0.083)	Cell proliferation (0.916) Immune response (0.334)	pINCY
44	543-587	Reproductive (0.192) Gastrointestinal (0.154) Nervous (0.154)	Cancer (0.385) Cell proliferation (0.308) Inflammation (0.077)	PBLUESCRIPT
45	545-589	Reproductive (0.220) Cardiovascular (0.171) Hematopoietic/Immune (0.159)	Cancer (0.366) Cell proliferation (0.354) Inflammation (0.293)	PBLUESCRIPT
46	165-209	Nervous (0.486) Gastrointestinal (0.143) Reproductive (0.143)	Cancer (0.343) Inflammation (0.228) Trauma (0.200)	PSPORT1

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
47	327-371	Cardiovascular (0.213) Reproductive (0.213) Gastrointestinal (0.128) Nervous (0.128)	Cancer (0.532) Cell proliferation (0.170) Inflammation (0.106)	PSPORT1
48	541-585	Cardiovascular (0.400) Hematopoietic/Immune (0.200) Nervous (0.200) Reproductive (0.200)	Cancer (0.800)	pINCY
49	326-370	Reproductive (0.278) Hematopoietic/Immune (0.167) Gastrointestinal (0.167)	Cancer (0.500) Inflammation (0.222) Cell proliferation (0.167)	pINCY
50	304-351	Reproductive (0.378) Gastrointestinal (0.178) Hematopoietic/Immune (0.089) Urologic (0.089)	Cancer (0.489) Inflammation (0.222) Cell proliferation (0.178)	pINCY
51	36-80	Nervous (0.273) Cardiovascular (0.182) Reproductive (0.227)	Cancer (0.591) Inflammation (0.182) Cell proliferation (0.045)	pINCY
52	236-280	Gastrointestinal (0.273) Nervous (0.212) Reproductive (0.182)	Cancer (0.364) Inflammation (0.242) Cell proliferation (0.121)	pINCY
53	435-479	Reproductive (0.303) Cardiovascular (0.167) Nervous (0.152)	Cancer (0.500) Inflammation (0.152) Trauma (0.106)	PSPORT1
54	326-370	Reproductive (0.276) Hematopoietic/Immune (0.207) Cardiovascular (0.143)	Cancer (0.379) Inflammation (0.276) Cell proliferation (0.138)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
55	834-878	Reproductive (0.261) Nervous (0.188) Cardiovascular (0.159)	Cancer (0.333) Cell proliferation (0.218) Inflammation (0.188)	pINCY
56	273-317	Cardiovascular (0.417) Nervous (0.250) Reproductive (0.167)	Inflammation (0.333) Cancer (0.250) Cell proliferation (0.167)	pINCY
57	327-371	Gastrointestinal (0.400) Reproductive (0.200)	Cancer (0.560) Inflammation (0.240) Cell proliferation (0.120)	pINCY
58	444-488	Nervous (0.180) Hematopoietic/Immune (0.156) Reproductive (0.156)	Cancer (0.426) Inflammation (0.221) Cell proliferation (0.131)	pINCY

Table 4

Polynucleotide SEQ ID NO:	Library	Library Comment
30	BLADTUT02	Library was constructed using RNA isolated from bladder tumor tissue removed from an 80-year-old Caucasian female during a radical cystectomy and lymph node excision. Pathology indicated grade 3 invasive transitional cell carcinoma. Family history included acute renal failure, osteoarthritis, and atherosclerosis.
31	LUNGNOT09	Library was constructed using RNA isolated from the lung tissue of a 23-week-old Caucasian male fetus. The pregnancy was terminated following a diagnosis by ultrasound of infantile polycystic kidney disease.
32	BRAINOT12	Library was constructed using RNA isolated from brain tissue removed from the right frontal lobe of a 5-year-old Caucasian male during a hemispherectomy. Pathology indicated extensive polymicrogyria and mild to moderate gliosis (predominantly subpial and subcortical), which are consistent with chronic seizure disorder. Family history included a cervical neoplasm.
33	COLNNOT23	Library was constructed using RNA isolated from diseased colon tissue removed from a 16-year-old Caucasian male during a total colectomy with abdominal/perineal resection. Pathology indicated gastritis and pancolitis consistent with the acute phase of ulcerative colitis. Inflammation was more severe in the transverse colon, with inflammation confined to the mucosa. There was only mild involvement of the ascending and sigmoid colon, and no significant involvement of the cecum, rectum, or terminal ileum. Family history included irritable bowel syndrome.
34	COLNNOT23	Library was constructed using RNA isolated from diseased colon tissue removed from a 16-year-old Caucasian male during a total colectomy with abdominal/perineal resection. Pathology indicated gastritis and pancolitis consistent with the acute phase of ulcerative colitis. Inflammation was more severe in the transverse colon, with inflammation confined to the mucosa. There was only mild involvement of the ascending and sigmoid colon, and no significant involvement of the cecum, rectum, or terminal ileum. Family history included irritable bowel syndrome.

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
35	COLNNOT27	Library was constructed using RNA isolated from diseased cecal tissue removed from 31-year-old Caucasian male during a total intra-abdominal colectomy, appendectomy, and permanent ileostomy. Pathology indicated severe active Crohn's disease involving the colon from the cecum to the rectum. There were deep rake-like ulcerations which spared the intervening mucosa. The ulcers extended into the muscularis, and there was transmural inflammation. Patient history included an irritable colon. Previous surgeries included a colonoscopy.
36	BEPINOT01	Library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
37	THP1NOT03	Library was constructed using RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia.
38	BRSTTUT14	Library was constructed using RNA isolated from breast tumor tissue removed from a 62-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated an invasive grade 3 (of 4), nuclear grade 3 (of 3) adenocarcinoma, ductal type. Ductal carcinoma in situ, comedo type, comprised 60% of the tumor mass. Metastatic adenocarcinoma was identified in one (of 14) axillary lymph nodes with no perinodal extension. Tumor cells were strongly positive for estrogen receptors and weakly positive for progesterone receptors. Patient history included benign colon neoplasm, hyperlipidemia, cardiac dysrhythmia, and obesity. Family history included atherosclerotic coronary artery disease, myocardial infarction, colon cancer, ovarian cancer, lung cancer, and cerebrovascular disease.
39	EPIGNOT01	Library was constructed using RNA isolated from epiglottic tissue removed from a 71-year-old male during laryngectomy with right parathyroid biopsy. Pathology for the associated tumor tissue indicated recurrent grade 1 papillary thyroid carcinoma.

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
40	KIDNTUT16	Library was constructed using RNA isolated from left pole kidney tumor tissue removed from a 53-year-old Caucasian female during a nephroureterectomy. Pathology indicated grade 2 renal cell carcinoma. Patient history included hyperlipidemia, cardiac dysrhythmia, metrorrhagia, cerebrovascular disease, atherosclerotic coronary artery disease. Family history included cerebrovascular disease and atherosclerotic coronary artery disease.
41	BRAXNOT02	Library was constructed using RNA isolated from cerebellar tissue removed from a 64-year-old male. Patient history included carcinoma of the left bronchus.
42	KIDNNOT26	Library was constructed using RNA isolated from left kidney medulla and cortex tissue removed from a 53-year-old Caucasian female during a nephroureterectomy. Pathology for the associated tumor tissue indicated grade 2 renal cell carcinoma involving the lower pole of the kidney. Patient history included hyperlipidemia, cardiac dysrhythmia, menorrhagia, normal delivery, cerebrovascular disease, and atherosclerotic coronary artery disease. Family history included cerebrovascular disease and atherosclerotic coronary artery disease.
43	MONOTXT02	Library was constructed using RNA isolated from treated monocytes from peripheral blood removed from a 42-year-old female. The cells were treated with interleukin-10 (IL-10) and lipopolysaccharide (LPS). IL-10 was added at time 0 at 10 ng/ml, LPS was added at 1 hour at 5 ng/ml. The monocytes were isolated from buffy coat by adherence to plastic. Incubation time was 24 hours.
44	HEARNOT01	Library was constructed using RNA isolated from the whole heart tissue of a 56-year-old male, who died from an intracranial bleed.
45	HNT2RAT01	Library was constructed at Stratagene (STR937231), using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated with retinoic acid for 24 hours

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
46	SYNOOAT01	Library was constructed using RNA isolated from the knee synovial membrane tissue of an 82-year-old female with osteoarthritis.
47	MYOMNOT01	Library was constructed using RNA isolated from uterine myometrial tissue removed from a 43-year-old Caucasian female during a vaginal hysterectomy and removal of the fallopian tubes and ovaries. Family history included lung cancer, stroke, type II diabetes, hepatic lesion, chronic liver disease, hyperlipidemia, congenital heart anomaly, and mitral valve prolapse.
48	BRAITUT08	Library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 47-year-old Caucasian male during excision of cerebral meningeal tissue. Pathology indicated grade 4 fibrillary astrocytoma with focal tumoral radionecrosis. Patient history included cerebrovascular disease, deficiency anemia, hyperlipidemia, epilepsy, and tobacco use. Family history included cerebrovascular disease and a malignant prostate neoplasm.
49	BRAINOT14	Library was constructed using RNA isolated from brain tissue removed from the left frontal lobe of a 40-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated grade 4 gemistocytic astrocytoma.
50	COLNPOT01	Library was constructed using RNA isolated from colon polyp tissue removed from a 40-year-old Caucasian female during a total colectomy. Pathology indicated an inflammatory pseudopolyp; this tissue was associated with a focally invasive grade 2 adenocarcinoma and multiple tubovillous adenomas. Patient history included a benign neoplasm of the bowel.
51	CORPNOT02	Library was constructed using RNA isolated from diseased corpus callosum tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
52	ENDCNOT01	Library was constructed using RNA isolated from endothelial cells removed from the coronary artery of a 58-year-old Hispanic male.

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
53	BRSTNOT05	Library was constructed using RNA isolated from breast tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated multicentric invasive grade 4 lobular carcinoma. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular and cardiovascular disease, breast and prostate cancer, and type I diabetes.
54	CONUTUT01	Library was constructed using RNA isolated from sigmoid mesentery tumor tissue obtained from a 61-year-old female during a total abdominal hysterectomy and bilateral salpingo-oophorectomy with regional lymph node excision. Pathology indicated a metastatic grade 4 malignant mixed mullerian tumor present in the sigmoid mesentery at two sites.
55	UTRSNOT11	Library was constructed using RNA isolated from uterine myometrial tissue removed from a 43-year-old female during a vaginal hysterectomy and removal of the fallopian tubes and ovaries. Pathology for the associated tumor tissue indicated that the myometrium contained an intramural and a submucosal leiomyoma. Family history included benign hypertension, hyperlipidemia, colon cancer, type II diabetes, and atherosclerotic coronary artery disease.
56	ENDCNOT04	Library was constructed using RNA isolated from coronary artery endothelial cell tissue removed from a 3-year-old Caucasian male.

[illegible][illegible]

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score \geq GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <i>supra</i> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
 - 5 a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-23 and SEQ ID NO:25-29,
 - b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-23 and SEQ ID NO:25-29,
 - c) a biologically active fragment of an amino acid sequence selected from the group
 - 10 consisting of SEQ ID NO:1-23 and SEQ ID NO:25-29, and
 - d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-23 and SEQ ID NO:25-29.
2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1-23
- 15 and SEQ ID NO:25-29.
3. An isolated polynucleotide encoding a polypeptide of claim 1.
4. An isolated polynucleotide of claim 3 selected from the group consisting of SEQ ID
- 20 NO:30-52 and SEQ ID NO:54-58.
5. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.
- 25 6. A cell transformed with a recombinant polynucleotide of claim 5.
7. A transgenic organism comprising a recombinant polynucleotide of claim 5.
8. A method for producing a polypeptide of claim 1, the method comprising:
 - 30 a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and
 - b) recovering the polypeptide so expressed.
- 35

WO 00/56891

PCT/US00/07817

9. An isolated antibody which specifically binds to a polypeptide of claim 1.
10. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:
 - 5 a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:30-52 and SEQ ID NO:54-58,
 - b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:30-52 and SEQ ID NO:54-58,
 - 10 c) a polynucleotide sequence complementary to a),
 - d) a polynucleotide sequence complementary to b), and
 - e) an RNA equivalent of a)-d).
11. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a
15 polynucleotide of claim 10.
12. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 10, the method comprising:
 - 20 a) hybridizing the sample with a probe comprising at least 16 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and
 - b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.
- 25 13. A method of claim 12, wherein the probe comprises at least 30 contiguous nucleotides.
14. A method of claim 12, wherein the probe comprises at least 60 contiguous nucleotides.
- 30 15. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.
16. A method for treating a disease or condition associated with decreased expression of functional HTMP, comprising administering to a patient in need of such treatment the pharmaceutical
35 composition of claim 15.

WO 00/56891

PCT/US00/07817

17. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting agonist activity in the sample.

5

18. A pharmaceutical composition comprising an agonist compound identified by a method of claim 17 and a pharmaceutically acceptable excipient.

19. A method for treating a disease or condition associated with decreased expression of functional HTMP, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 18.

20. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

15

21. A pharmaceutical composition comprising an antagonist compound identified by a method of claim 20 and a pharmaceutically acceptable excipient.

20

22. A method for treating a disease or condition associated with overexpression of functional HTMP, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 21.

23. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 4, the method comprising:

25

- a) exposing a sample comprising the target polynucleotide to a compound, and
- b) detecting altered expression of the target polynucleotide.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 September 2000 (28.09.2000)

PCT

(10) International Publication Number
WO 00/56891 A3

(51) International Patent Classification⁷: C12N 15/12,
C07K 14/47, C12N 5/10, C12P 21/00, C07K 16/18, A61K
38/17, C12Q 1/68

(21) International Application Number: PCT/US00/07817

(22) International Filing Date: 22 March 2000 (22.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/125,537 22 March 1999 (22.03.1999) US
60/139,565 16 June 1999 (16.06.1999) US

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier applications:

US	60/125,537 (CIP)
Filed on	22 March 1999 (22.03.1999)
US	60/139,565 (CIP)
Filed on	16 June 1999 (16.06.1999)

(71) Applicant (for all designated States except US): INCYTE
PHARMACEUTICALS, INC. [US/US]; 3160 Porter
Drive, Palo Alto, CA 94304 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): YUE, Henry
[US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US).
LAL, Preeti [IN/US]; 2382 Lass Drive, Santa Clara, CA
95054 (US). TANG, Y., Tom [CN/US]; 4230 Ranwick
Court, San Jose, CA 95118 (US). HILLMAN, Jennifer,
L. [US/US]; 230 Monroe Drive, #12, Mountain View, CA
94040 (US). REDDY, Roopa [IN/US]; 1233 W. McKinley
Drive, Sunnyvale, CA 94086 (US). BANDMAN, Olga

[US/US]; 366 Anna Avenue, Mountain View, CA 94043
(US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago
Road, San Leandro, CA 94577 (US). LU, Dyung, Aina,
M. [US/US]; 55 Park Belmont Place, San Jose, CA 95136
(US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs
Drive, Hayward, CA 94545 (US). YANG, Junming
[CN/US]; 7125 Bark Lane, San Jose, CA 95129 (US).

(74) Agents: HAMLET-COX, Diana et al.; Incyte Pharma-
ceuticals, Inc., 3160 Porter Drive, Palo Alto, CA 94304
(US).

(81) Designated States (national): AE, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE,
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,
MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ,
VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report

(88) Date of publication of the international search report:
5 April 2001

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette

(54) Title: HUMAN TRANSMEMBRANE PROTEINS

(57) Abstract: The invention provides human transmembrane proteins (HTMP) and polynucleotides which identify and encode HTMP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of HTMP.



WO 00/56891 A3

Docket No.: PF-0681 USN

**DECLARATION AND POWER OF ATTORNEY FOR
UNITED STATES PATENT APPLICATION**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

HUMAN TRANSMEMBRANE PROTEINS

the specification of which:

/___/ is attached hereto.

/___/ was filed on _____ as application Serial No. _____ and if this box contains an X /___/, was amended on _____.

/X___/ was filed as Patent Cooperation Treaty international application No. **PCT/US00/07817** on **March 22, 2000**, if this box contains an X /___/, was amended on under Patent Cooperation Treaty Article 19 on _____ 2001, and if this box contains an X /___/, was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge my duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim the benefit under Title 35, United States Code, §119 or §365(a)-(b) of any foreign application(s) for patent or inventor's certificate indicated below and of any Patent Cooperation Treaty international applications(s) designating at least one country other than the United States indicated below and have also identified below any foreign application(s) for patent or inventor's certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application for said subject matter the priority of which is claimed:

Docket No.: PF-0681 USN

Country	Number	Filing Date	Priority Claimed
_____	_____	_____	// Yes // No
_____	_____	_____	// Yes // No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Application Serial No.	Filed	Status (Pending, Abandoned, Patented)
60/125,537	March 22, 1999	Expired
60/139,565	June 16, 1999	Expired

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of Title 35, United States Code §112, I acknowledge my duty to disclose material information as defined in Title 37 Code of Federal Regulations, §1.56(a) which occurred between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

Application Serial No.	Filed	Status (Pending, Abandoned, Patented)
_____	_____	_____

I hereby appoint the following:

Lucy J. Billings	Reg. No. <u>36,749</u>
Michael C. Cerrone	Reg. No. <u>39,132</u>
Diana Hamlet-Cox	Reg. No. <u>33,302</u>
Richard C. Ekstrom	Reg. No. <u>37,027</u>
Barrie D. Greene	Reg. No. <u>46,740</u>
Matthew R. Kaser	Reg. No. <u>44,817</u>
Lynn E. Murry	Reg. No. <u>42,918</u>
Shirley A. Recipon	Reg. No. <u>47,016</u>
Susan K. Sather	Reg. No. <u>44,316</u>
Michelle M. Stempien	Reg. No. <u>41,327</u>
David G. Streeter	Reg. No. <u>43,168</u>
Stephen Todd	Reg. No. <u>47,139</u>
P. Ben Wang	Reg. No. <u>41,420</u>

respectively and individually, as my patent attorneys and/or agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

Docket No.: PF-0681 USN

**LEGAL DEPARTMENT
 INCYTE GENOMICS, INC.
 3160 PORTER DRIVE, PALO ALTO, CA 94304**

TEL: 650-855-0555 FAX: 650-849-8886 or 650-845-4166

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

First Joint Inventor: *100*


Full name:	<u>Henry Yue</u>
Signature:	<u><i>Henry Yue</i></u>
Date:	<u>September 24</u> , 2001
Citizenship	United States of America
Residence:	<u>Sunnyvale, California CA</u>
P.O. Address:	<u>826 Lois Avenue</u> <u>Sunnyvale, California 94087</u>

Second Joint Inventor: *200*

Full name:	<u>Preeti Lal</u>
Signature:	<u><i>Preeti Lal</i></u>
Date:	<u>September 10</u> , 2001
Citizenship	India
Residence:	<u>Santa Clara, California CA</u>
P.O. Address:	<u>P.O. Box 5142</u> <u>Santa Clara, California 95056</u>

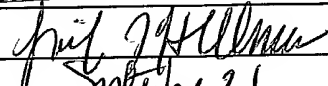
Docket No.: PF-0681 USN

Third Joint Inventor: 300

Full name: Y. Tom Tang
Signature: 
Date: Sept. 10, 2001
Citizenship: United States of America
Residence: San Jose, California CA
P.O. Address: 4230 Ranwick Court
San Jose, California 95118

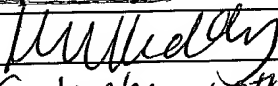
Fourth Joint Inventor:

400

Full name: Jennifer L. Hillman
Signature: 
Date: September 21, 2001
Citizenship: United States of America
Residence: Mountain View, California CA
P.O. Address: 230 Monroe Drive, #17,
Mountain View, California 94040

Fifth Joint Inventor:

500

Full name: Roopa Reddy
Signature: 
Date: September 10th, 2001
Citizenship: India
Residence: Sunnyvale, California CA
P.O. Address: 1233 W. McKinley Ave., #3
Sunnyvale, California 94086

Docket No.: PF-0681 USN

Sixth Joint Inventor:

6-00

Full name:

Olga Bandman

Signature:

Olga Bandman

Date:

12 September, 2001

Citizenship

United States of America

Residence:

Mountain View, California CA

P.O. Address:

366 Anna Avenue
Mountain View, CA 94043

Seventh Joint Inventor:

7-00

Full name:

Mariah R. Baughn

Signature:

Mariah R. Baughn

Date:

September 5, 2001

Citizenship

United States of America

Residence:

San Leandro, California CA

P.O. Address:

14244 Santiago Road
San Leandro, California 94577

Eighth Joint Inventor:

8-00

Full Name:

Dyung Aina M. Lu

Signature:

Dyung Aina M. Lu

Date:

September 7, 2001

Citizenship

United States of America

Residence:

San Jose, California CA

P.O. Address:

233 Coy Drive
San Jose, California 95123

Docket No.: PF-0681 USN

Ninth Joint Inventor:

900

Full name:

Yalda Azimzai

Signature:

Yalda Azimzai

Date:

September 13, 2001

Citizenship

United States of America

Residence:

San Jose, California CA

P.O. Address:

5518 Boulder Canyon Drive
Castro Valley, California 94552

Tenth Joint Inventor:

1600

Full name:

Junming Yang

Signature:

Junming Yang

Date:

September 17, 2001

Citizenship

China

Residence:

San Jose, California CA

P.O. Address:

7125 Bark Lane
San Jose, California 95129

WO 00/56891

PCT/US00/07817

PF-0681 PCT

Sequence Listing

<110> INCYTE PHARMACEUTICALS, INC.

YUE, Henry
LAL, Preeti
TANG, Y. Tom
HILLMAN, Jennifer L.
REDDY, Roopa
BANDMAN, Olga
BAUGHN, Mariah R.
Lu, Dyung Aina L.
AZIMZAI, Yalda
YANG, Junming

<120> HUMAN TRANSMEMBRANE PROTEINS

<130> PF-0681 PCT

<140> To Be Assigned

<141> Herewith

<150> 60/125,537; 60 139,565

<151> 1999-03-22; 1999-06-16

<160> 58

<170> PERL Program

<210> 1

<211> 417

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1316927CD1

<400> 1

Met	Trp	Lys	Gly	Leu	Val	Lys	Arg	Asn	Ala	Ser	Val	Glu	Thr	Val
1				5					10					15
Asp	Asn	Lys	Thr	Ser	Glu	Asp	Val	Thr	Met	Ala	Ala	Ala	Ser	Pro
				20					25					30
Val	Thr	Leu	Thr	Lys	Gly	Thr	Ser	Ala	Ala	His	Leu	Asn	Ser	Met
				35					40					45
Glu	Val	Thr	Thr	Glu	Asp	Thr	Ser	Arg	Thr	Asp	Val	Ser	Glu	Pro
				50					55					60
Ala	Thr	Ser	Gly	Gly	Ala	Ala	Asp	Gly	Val	Thr	Ser	Ile	Ala	Pro
				65					70					75
Thr	Ala	Val	Ala	Ser	Ser	Thr	Thr	Ala	Ala	Ser	Ile	Thr	Thr	Ala
				80					85					90
Ala	Ser	Ser	Met	Thr	Val	Ala	Ser	Ser	Ala	Pro	Thr	Thr	Ala	Ala
				95					100					105
Ser	Ser	Thr	Thr	Val	Ala	Ser	Ile	Ala	Pro	Thr	Thr	Ala	Ala	Ser
				110					115					120
Ser	Met	Thr	Ala	Ala	Ser	Ser	Thr	Pro	Met	Thr	Leu	Ala	Leu	Pro
				125					130					135
Ala	Pro	Thr	Ser	Thr	Ser	Thr	Gly	Arg	Thr	Pro	Ser	Thr	Thr	Ala
				140					145					150
Thr	Gly	His	Pro	Ser	Leu	Ser	Thr	Ala	Leu	Ala	Gln	Val	Pro	Lys
				155					160					165

PF-0681 PCT

[illegible]

```
<210> 3
<211> 273
<212> PRT
<213> Homo sapiens
```

```
<220>  
<221> misc_feature  
<223> Incyte ID No: 1415487CD1
```

<400>	3														
Met	Ile	Leu	Ser	Ser	Tyr	Phe	Ile	Asn	Phe	Ile	Tyr	Leu	Ala	Lys	
1				5					10					15	
Ser	Thr	Lys	Lys	Thr	Met	Leu	Thr	Leu	Thr	Leu	Val	Cys	Ala	Ile	
				20					25					30	
Thr	Phe	Leu	Leu	Val	Cys	Ser	Gly	Thr	Phe	Phe	Pro	Tyr	Ser	Ser	
				35					40					45	
Asn	Pro	Ala	Asn	Pro	Lys	Pro	Lys	Arg	Val	Phe	Leu	Gln	His	Met	
				50					55					60	
Thr	Arg	Thr	Phe	His	Asp	Leu	Glu	Gly	Asn	Ala	Val	Lys	Arg	Asp	
				65					70					75	
Ser	Gly	Ile	Trp	Ile	Asn	Gly	Phe	Asp	Tyr	Thr	Gly	Ile	Ser	His	
				80					85					90	
Ile	Thr	Pro	His	Ile	Pro	Glu	Ile	Asn	Asp	Ser	Ile	Arg	Ala	His	
				95					100					105	
Cys	Glu	Glu	Asn	Ala	Pro	Leu	Cys	Gly	Phe	Pro	Trp	Tyr	Leu	Pro	
				110					115					120	
Val	His	Phe	Leu	Ile	Arg	Lys	Asn	Trp	Tyr	Leu	Pro	Ala	Pro	Glu	
				125					130					135	
Val	Ser	Pro	Arg	Asn	Pro	Pro	His	Phe	Arg	Leu	Ile	Ser	Lys	Glu	
				140					145					150	
Gln	Thr	Pro	Trp	Asp	Ser	Ile	Lys	Leu	Thr	Phe	Glu	Ala	Thr	Gly	
				155					160					165	
Pro	Ser	His	Met	Ser	Phe	Tyr	Val	Arg	Ala	His	Lys	Gly	Ser	Thr	
				170					175					180	

WO 00/56891

PCT/US00/07817

PF-0681 PCT

Leu	Ser	Gln	Trp	Ser	Leu	Gly	Asn	Gly	Thr	Pro	Val	Thr	Ser	Lys
				185					190					195
Gly	Gly	Asp	Tyr	Phe	Val	Phe	Tyr	Ser	His	Gly	Leu	Gln	Ala	Ser
				200					205					210
Ala	Trp	Gln	Phe	Trp	Ile	Glu	Val	Gln	Val	Ser	Glu	Glu	His	Pro
				215					220					225
Glu	Gly	Met	Val	Thr	Val	Ala	Ile	Ala	Ala	His	Tyr	Leu	Ser	Gly
				230					235					240
Glu	Asp	Lys	Arg	Ser	Pro	Gln	Leu	Asp	Ala	Leu	Lys	Glu	Lys	Phe
				245					250					255
Pro	Asp	Trp	Thr	Phe	Pro	Ser	Ala	Trp	Val	Cys	Thr	Tyr	Asp	Leu
				260					265					270
Phe	Val	Phe												

<210> 4
 <211> 222
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1693184CD1

<400> 4	
Met Cys Leu Arg Leu Gly Gly Leu Ser Val Gly Asp Phe Arg Lys	
1 5 10 15	
Val Leu Met Lys Thr Gly Leu Val Leu Val Val Leu Gly His Val	
20 25 30	
Ser Phe Ile Thr Ala Ala Leu Phe His Gly Thr Val Leu Arg Tyr	
35 40 45	
Val Gly Thr Pro Gln Asp Ala Val Ala Leu Gln Tyr Cys Val Val	
50 55 60	
Asn Ile Leu Ser Val Thr Ser Ala Ile Val Val Ile Thr Ser Gly	
65 70 75	
Ile Ala Ala Ile Val Leu Ser Arg Tyr Leu Pro Ser Thr Pro Leu	
80 85 90	
Arg Trp Thr Val Phe Ser Ser Ser Val Ala Cys Ala Leu Leu Ser	
95 100 105	
Leu Thr Cys Ala Leu Gly Leu Leu Ala Ser Ile Ala Met Thr Phe	
110 115 120	
Ala Thr Gln Gly Lys Ala Leu Leu Ala Ala Cys Thr Phe Gly Ser	
125 130 135	
Ser Glu Leu Leu Ala Leu Ala Pro Asp Cys Pro Phe Asp Pro Thr	
140 145 150	
Arg Ile Tyr Ser Ser Ser Leu Cys Leu Trp Gly Ile Ala Leu Val	
155 160 165	
Leu Cys Val Ala Glu Asn Val Phe Ala Val Arg Cys Ala Gln Leu	
170 175 180	
Thr His Gln Leu Leu Glu Leu Arg Pro Trp Trp Gly Lys Ser Ser	
185 190 195	
His His Met Met Arg Glu Asn Pro Glu Leu Val Glu Gly Arg Asp	
200 205 210	
Leu Leu Ser Cys Thr Ser Ser Glu Pro Leu Thr Leu	
215 220	

<210> 5
 <211> 329
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature

WO 00/56891

PCT/US00/07817

PF-0681 PCT

<223> Incyte ID No: 1695049CD1

<400> 5

Met	Pro	Gly	Lys	His	Gln	His	Phe	Gln	Glu	Pro	Glu	Val	Gly	Cys
1				5					10					15
Cys	Gly	Lys	Tyr	Phe	Leu	Phe	Gly	Phe	Asn	Ile	Val	Phe	Trp	Val
				20					25					30
Leu	Gly	Ala	Leu	Phe	Leu	Ala	Ile	Gly	Leu	Trp	Ala	Trp	Gly	Glu
				35					40					45
Lys	Gly	Val	Leu	Ser	Asn	Ile	Ser	Ala	Leu	Thr	Asp	Leu	Gly	Gly
				50					55					60
Leu	Asp	Pro	Val	Trp	Leu	Phe	Val	Val	Val	Gly	Gly	Val	Met	Ser
				65					70					75
Val	Leu	Gly	Phe	Ala	Gly	Cys	Ile	Gly	Ala	Leu	Arg	Glu	Asn	Thr
				80					85					90
Phe	Leu	Leu	Lys	Phe	Phe	Ser	Val	Phe	Leu	Gly	Leu	Ile	Phe	Phe
				95					100					105
Leu	Glu	Leu	Ala	Thr	Gly	Ile	Leu	Ala	Phe	Val	Phe	Lys	Asp	Trp
				110					115					120
Ile	Arg	Asp	Gln	Leu	Asn	Leu	Phe	Ile	Asn	Asn	Val	Lys	Ala	Ala
				125					130					135
Tyr	Arg	Asp	Asp	Ile	Asp	Leu	Gln	Asn	Leu	Ile	Asp	Phe	Ala	Gln
				140					145					150
Glu	Tyr	Trp	Ser	Cys	Cys	Gly	Ala	Arg	Gly	Pro	Asn	Asp	Trp	Asn
				155					160					165
Leu	Asn	Ile	Tyr	Phe	Asn	Cys	Thr	Asp	Leu	Asn	Pro	Ser	Arg	Glu
				170					175					180
Arg	Cys	Gly	Val	Pro	Phe	Ser	Cys	Cys	Val	Arg	Asp	Pro	Ala	Glu
				185					190					195
Asp	Val	Leu	Asn	Thr	Gln	Cys	Gly	Tyr	Asp	Val	Arg	Leu	Lys	Leu
				200					205					210
Glu	Leu	Glu	Gln	Gln	Gly	Phe	Ile	His	Thr	Lys	Gly	Cys	Val	Gly
				215					220					225
Gln	Phe	Glu	Lys	Trp	Leu	Gln	Asp	Asn	Leu	Ile	Val	Val	Ala	Gly
				230					235					240
Val	Phe	Met	Gly	Ile	Ala	Leu	Leu	Gln	Ile	Phe	Gly	Ile	Cys	Leu
				245					250					255
Ala	Gln	Asn	Leu	Val	Ser	Asp	Ile	Lys	Ala	Val	Lys	Ala	Asn	Trp
				260					265					270
Ser	Lys	Trp	Asn	Asp	Asp	Phe	Glu	Asn	His	Trp	Leu	Thr	Pro	Thr
				275					280					285
Ile	Ser	Glu	Val	Leu	Ser	Thr	Ala	Gly	Pro	Gln	Gln	Asn	Ser	Leu
				290					295					300
Thr	Gly	Ala	Pro	Gly	Pro	Ala	Pro	Pro	Ser	Arg	His	Val	Phe	Phe
				305					310					315
Gly	Leu	Gly	Gly	Leu	Tyr	Pro	Glu	Pro	Thr	Phe	Lys	Asn	Trp	
				320					325					

<210> 6

<211> 351

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1802448CD1

<400> 6

Met	Ala	Leu	Thr	Gly	Ala	Ser	Asp	Pro	Ser	Ala	Glu	Ala	Glu	Ala
1				5					10					15
Asn	Gly	Glu	Lys	Pro	Phe	Leu	Leu	Arg	Ala	Leu	Gln	Ile	Ala	Leu
				20					25					30

WO 00/56891

PCT/US00/07817

PF-0681 PCT

				50					55					60
Asn	Lys	Ile	Ala	Leu	Glu	Leu	Cys	Thr	Phe	Thr	Leu	Ala	Ile	Ala
				65					70					75
Leu	Gly	Ala	Val	Leu	Leu	Leu	Pro	Phe	Ser	Ile	Ile	Ser	Asn	Glu
				80					85					90
Val	Leu	Leu	Ser	Leu	Pro	Arg	Asn	Tyr	Tyr	Ile	Gln	Trp	Leu	Asn
				95					100					105
Gly	Ser	Leu	Ile	His	Gly	Leu	Trp	Asn	Leu	Val	Phe	Leu	Phe	Ser
				110					115					120
Asn	Leu	Ser	Leu	Ile	Phe	Leu	Met	Pro	Phe	Ala	Tyr	Phe	Phe	Thr
				125					130					135
Glu	Ser	Glu	Gly	Phe	Ala	Gly	Ser	Arg	Lys	Gly	Val	Leu	Gly	Arg
				140					145					150
Val	Tyr	Glu	Thr	Val	Val	Met	Leu	Met	Leu	Leu	Thr	Leu	Leu	Val
				155					160					165
Leu	Gly	Met	Val	Trp	Val	Ala	Ser	Ala	Ile	Val	Asp	Lys	Asn	Lys
				170					175					180
Ala	Asn	Arg	Glu	Ser	Leu	Tyr	Asp	Phe	Trp	Glu	Tyr	Tyr	Leu	Pro
				185					190					195
Tyr	Leu	Tyr	Ser	Cys	Ile	Ser	Phe	Leu	Gly	Val	Leu	Leu	Leu	Leu
				200					205					210
Val	Cys	Thr	Pro	Leu	Gly	Leu	Ala	Arg	Met	Phe	Ser	Val	Thr	Gly
				215					220					225
Lys	Leu	Leu	Val	Lys	Pro	Arg	Leu	Leu	Glu	Asp	Leu	Glu	Glu	Gln
				230					235					240
Leu	Tyr	Cys	Ser	Ala	Phe	Glu	Glu	Ala	Ala	Leu	Thr	Arg	Arg	Ile
				245					250					255
Cys	Asn	Pro	Thr	Ser	Cys	Trp	Leu	Pro	Leu	Asp	Met	Glu	Leu	Leu
				260					265					270
His	Arg	Gln	Val	Leu	Ala	Leu	Gln	Thr	Gln	Arg	Val	Leu	Leu	Glu
				275					280					285
Lys	Arg	Arg	Lys	Ala	Ser	Ala	Trp	Gln	Arg	Asn	Leu	Gly	Tyr	Pro
				290					295					300
Leu	Ala	Met	Leu	Cys	Leu	Leu	Val	Leu	Thr	Gly	Leu	Ser	Val	Leu
				305					310					315
Ile	Val	Ala	Ile	His	Ile	Leu	Glu	Leu	Leu	Ile	Asp	Glu	Ala	Ala
				320					325					330
Met	Pro	Arg	Gly	Met	Gln	Gly	Thr	Ser	Leu	Gly	Gln	Val	Ser	Phe
				335					340					345
Ser	Lys	Leu	Gly	Ser	Phe	Gly	Ala	Val	Ile	Gln	Val	Val	Leu	Ile
				350					355					360
Phe	Tyr	Leu	Met	Val	Ser	Ser	Val	Val	Gly	Phe	Tyr	Ser	Ser	Pro
				365					370					375
Leu	Phe	Arg	Ser	Leu	Arg	Pro	Arg	Trp	His	Asp	Thr	Ala	Met	Thr
				380					385					390
Gln	Ile	Ile	Gly	Asn	Cys	Val	Cys	Leu	Leu	Val	Leu	Ser	Ser	Ala
				395					400					405
Leu	Pro	Val	Phe	Ser	Arg	Thr	Leu	Gly	Leu	Thr	Arg	Phe	Asp	Leu
				410					415					420
Leu	Gly	Asp	Phe	Gly	Arg	Phe	Asn	Trp	Leu	Gly	Asn	Phe	Tyr	Ile
				425					430					435
Val	Phe	Leu	Tyr	Asn	Ala	Ala	Phe	Ala	Gly	Leu	Thr	Thr	Leu	Cys
				440					445					450
Leu	Val	Lys	Thr	Phe	Thr	Ala	Ala	Val	Arg	Ala	Glu	Leu	Ile	Arg
				455					460					465
Ala	Phe	Gly	Leu	Asp	Arg	Leu	Pro	Leu	Pro	Val	Ser	Gly	Phe	Pro
				470					475					480
Gln	Ala	Ser	Arg	Lys	Thr	Gln	His	Gln						
				485										

<210> 8

<211> 291

WO 00/56891

PCT/US00/07817

PF-0681 PCT

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2448177CD1

<400> 8

```

Met Val Trp Lys Lys Leu Gly Ser Arg Asn Phe Ser Ser Cys Pro
 1          5          10          15
Ser Gly Ser Ile Gln Trp Ile Trp Asp Val Leu Gly Glu Cys Ala
          20          25          30
Gln Asp Gly Trp Asp Glu Ala Ser Val Gly Leu Gly Leu Ile Ser
          35          40          45
Ile Leu Cys Phe Ala Ala Ser Thr Phe Pro Gln Phe Ile Lys Ala
          50          55          60
Tyr Lys Thr Gly Asn Met Asp Gln Ala Leu Ser Leu Trp Phe Leu
          65          70          75
Leu Gly Trp Ile Gly Gly Asp Ser Cys Asn Leu Ile Gly Ser Phe
          80          85          90
Leu Ala Asp Gln Leu Pro Leu Gln Thr Tyr Thr Ala Val Tyr Tyr
          95          100          105
Val Leu Ala Asp Leu Val Met Leu Thr Leu Tyr Phe Tyr Tyr Lys
          110          115          120
Phe Arg Thr Arg Pro Ser Leu Leu Ser Ala Pro Ile Asn Ser Val
          125          130          135
Leu Leu Phe Leu Met Gly Met Ala Cys Ala Thr Pro Leu Leu Ser
          140          145          150
Ala Ala Gly Pro Val Ala Ala Pro Arg Glu Ala Phe Arg Gly Arg
          155          160          165
Ala Leu Leu Ser Val Glu Ser Gly Ser Lys Pro Phe Thr Arg Gln
          170          175          180
Glu Val Ile Gly Phe Val Ile Gly Ser Ile Ser Ser Val Leu Tyr
          185          190          195
Leu Leu Ser Arg Leu Pro Gln Ile Arg Thr Asn Phe Leu Arg Lys
          200          205          210
Ser Thr Gln Gly Ile Ser Tyr Ser Leu Phe Ala Leu Val Met Leu
          215          220          225
Gly Asn Thr Leu Tyr Gly Leu Ser Val Leu Leu Lys Asn Pro Glu
          230          235          240
Glu Gly Gln Ser Glu Gly Ser Tyr Leu Leu His His Leu Pro Trp
          245          250          255
Leu Val Gly Ser Leu Gly Val Leu Leu Leu Asp Thr Ile Ile Ser
          260          265          270
Ile Gln Phe Leu Val Tyr Arg Arg Ser Thr Ala Ala Ser Glu Leu
          275          280          285
Glu Pro Leu Leu Pro Ser
          290

```

<210> 9

<211> 172

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2741701CD1

<400> 9

```

Met Ser Ser Ser Gly Gly Ala Pro Gly Ala Ser Ala Ser Ser Ala
 1          5          10          15
Pro Pro Ala Gln Glu Glu Gly Met Thr Trp Trp Tyr Arg Trp Leu

```


WO 00/56891

PCT/US00/07817

PF-0681 PCT

<400> 11

Met	Leu	Cys	Ser	Leu	Leu	Leu	Cys	Glu	Cys	Leu	Leu	Leu	Val	Ala
1				5					10					15
Gly	Tyr	Ala	His	Asp	Asp	Asp	Trp	Ile	Asp	Pro	Thr	Asp	Met	Leu
				20					25					30
Asn	Tyr	Asp	Ala	Ala	Ser	Gly	Thr	Met	Arg	Lys	Ser	Gln	Ala	Lys
				35					40					45
Tyr	Gly	Ile	Ser	Gly	Glu	Lys	Asp	Val	Ser	Pro	Asp	Leu	Ser	Cys
				50					55					60
Ala	Asp	Glu	Ile	Ser	Glu	Cys	Tyr	His	Lys	Leu	Asp	Ser	Leu	Thr
				65					70					75
Tyr	Lys	Ile	Asp	Glu	Cys	Glu	Lys	Lys	Lys	Arg	Glu	Asp	Tyr	Glu
				80					85					90
Ser	Gln	Ser	Asn	Pro	Val	Phe	Arg	Arg	Tyr	Leu	Asn	Lys	Ile	Leu
				95					100					105
Ile	Glu	Ala	Gly	Lys	Leu	Gly	Leu	Pro	Asp	Glu	Asn	Lys	Gly	Asp
				110					115					120
Met	His	Tyr	Asp	Ala	Glu	Ile	Ile	Leu	Lys	Arg	Glu	Thr	Leu	Leu
				125					130					135
Glu	Ile	Gln	Lys	Phe	Leu	Asn	Gly	Glu	Asp	Trp	Lys	Pro	Gly	Ala
				140					145					150
Leu	Asp	Asp	Ala	Leu	Ser	Asp	Ile	Leu	Ile	Asn	Phe	Lys	Phe	His
				155					160					165
Asp	Phe	Glu	Thr	Trp	Lys	Trp	Arg	Phe	Glu	Asp	Ser	Phe	Gly	Val
				170					175					180
Asp	Pro	Tyr	Asn	Val	Leu	Met	Val	Leu	Leu	Cys	Leu	Leu	Cys	Ile
				185					190					195
Val	Val	Leu	Val	Ala	Thr	Glu	Leu	Trp	Thr	Tyr	Val	Arg	Trp	Tyr
				200					205					210
Thr	Gln	Leu	Arg	Arg	Val	Leu	Ile	Ile	Ser	Phe	Leu	Phe	Ser	Leu
				215					220					225
Gly	Trp	Asn	Trp	Met	Tyr	Leu	Tyr	Lys	Leu	Ala	Phe	Ala	Gln	His
				230					235					240
Gln	Ala	Glu	Val	Ala	Lys	Met	Glu	Pro	Leu	Asn	Asn	Val	Cys	Ala
				245					250					255
Lys	Lys	Met	Asp	Trp	Thr	Gly	Ser	Ile	Trp	Glu	Trp	Phe	Arg	Ser
				260					265					270
Ser	Trp	Thr	Tyr	Lys	Asp	Asp	Pro	Cys	Gln	Lys	Tyr	Tyr	Glu	Leu
				275					280					285
Leu	Leu	Val	Asn	Pro	Ile	Trp	Leu	Val	Pro	Pro	Thr	Lys	Ala	Leu
				290					295					300
Ala	Val	Thr	Phe	Thr	Thr	Phe	Val	Thr	Glu	Pro	Leu	Lys	His	Ile
				305					310					315
Gly	Lys	Gly	Thr	Gly	Glu	Phe	Ile	Lys	Ala	Leu	Met	Lys	Glu	Ile
				320					325					330
Pro	Ala	Leu	Leu	His	Leu	Pro	Val	Leu	Ile	Ile	Met	Ala	Leu	Ala
				335					340					345
Ile	Leu	Ser	Phe	Cys	Tyr	Gly	Ala	Gly	Lys	Ser	Val	His	Val	Leu
				350					355					360
Arg	His	Ile	Gly	Gly	Pro	Glu	Arg	Glu	Pro	Pro	Gln	Ala	Leu	Trp
				365					370					375
Pro	Arg	Asp	Arg	Arg	Arg	Gln	Glu	Glu	Ile	Asp	Tyr	Arg	Pro	Asp
				380					385					390
Gly	Gly	Ala	Gly	Asp	Ala	Asp	Phe	His	Tyr	Arg	Gly	Gln	Met	Gly
				395					400					405
Pro	Thr	Glu	Gln	Gly	Pro	Tyr	Ala	Lys	Thr	Tyr	Glu	Gly	Arg	Arg
				410					415					420
Glu	Ile	Leu	Arg	Glu	Arg	Asp	Val	Asp	Leu	Arg	Phe	Gln	Thr	Gly
				425					430					435
Asn	Lys	Ser	Pro	Glu	Val	Leu	Arg	Ala	Phe	Asp	Val	Pro	Asp	Ala
				440					445					450

WO 00/56891

PCT/US00/07817

PF-0681 PCT

Glu	Ala	Arg	Glu	His	Pro	Thr	Val	Val	Pro	Ser	His	Lys	Ser	Pro
				455					460					465
Val	Leu	Asp	Thr	Lys	Pro	Lys	Glu	Thr	Gly	Gly	Ile	Leu	Gly	Lys
				470					475					480
Ala	His	Arg	Lys	Lys	Ala	Val	Leu	Lys	Ala	Ala	Ser	Arg	Pro	Ser
				485					490					495
Leu	Ser	Leu	Ala	Lys	Thr	His	Gln	Gly	Ile	Gln	Lys	Val	His	Pro
				500					505					510
Gln	Arg	Lys	Arg	Pro	Ser	Ser	Ser	Leu	Lys	Pro	Gln	Ala	Ala	Gln
				515					520					525
Thr	Lys	Ala	Ala	His	Thr	Ala	Pro	Gln	Glu	Val	Trp	Leu	Asp	His
				530					535					540
Val	Asp	Arg	Ile	Arg	Ser	Ala	Ala	Pro	Val	Ala	Arg	Gly	Thr	Pro
				545					550					555
Ala	Gln	Thr	Thr	Ala	Ser	Ser	Leu	Leu	Arg	Ala	Leu	Tyr	Pro	Phe
				560					565					570
Gly	Asp	Glu	Val	Tyr	Phe	Asp	Ser							
				575										

<210> 12

<211> 313

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 4020882CD1

<400> 12

Met	Asp	Gly	Ile	Ile	Glu	Gln	Lys	Ser	Met	Leu	Val	His	Ser	Lys
1				5					10					15
Ile	Ser	Asp	Ala	Gly	Lys	Arg	Asn	Gly	Leu	Ile	Asn	Thr	Arg	Asn
				20					25					30
Leu	Met	Ala	Glu	Ser	Arg	Asp	Gly	Leu	Val	Ser	Val	Tyr	Pro	Ala
				35					40					45
Pro	Gln	Tyr	Gln	Ser	His	Arg	Val	Gly	Ala	Ser	Thr	Val	Pro	Ala
				50					55					60
Ser	Leu	Asp	Ser	Ser	Arg	Ser	Glu	Pro	Met	Gln	Gln	Leu	Leu	Asp
				65					70					75
Pro	Asn	Thr	Leu	Gln	Gln	Ser	Val	Glu	Ser	Arg	Tyr	Arg	Pro	Asn
				80					85					90
Ile	Ile	Leu	Tyr	Ser	Glu	Gly	Val	Leu	Arg	Ser	Trp	Gly	Asp	Gly
				95					100					105
Val	Ala	Ala	Asp	Cys	Cys	Glu	Thr	Thr	Phe	Ile	Glu	Asp	Arg	Ser
				110					115					120
Pro	Thr	Lys	Asp	Ser	Leu	Glu	Tyr	Pro	Asp	Gly	Lys	Phe	Ile	Asp
				125					130					135
Leu	Ser	Ala	Asp	Asp	Ile	Lys	Ile	His	Thr	Leu	Ser	Tyr	Asp	Val
				140					145					150
Glu	Glu	Glu	Glu	Glu	Phe	Gln	Glu	Leu	Glu	Ser	Asp	Tyr	Ser	Ser
				155					160					165
Asp	Thr	Glu	Ser	Glu	Asp	Asn	Phe	Leu	Met	Met	Pro	Pro	Arg	Asp
				170					175					180
His	Leu	Gly	Leu	Ser	Val	Phe	Ser	Met	Leu	Cys	Cys	Phe	Trp	Pro
				185					190					195
Leu	Gly	Ile	Ala	Ala	Phe	Tyr	Leu	Ser	His	Glu	Thr	Asn	Lys	Ala
				200					205					210
Val	Ala	Lys	Gly	Asp	Leu	His	Gln	Ala	Ser	Thr	Ser	Ser	Arg	Arg
				215					220					225
Ala	Leu	Phe	Leu	Ala	Val	Leu	Ser	Ile	Thr	Ile	Gly	Thr	Gly	Val
				230					235					240
Tyr	Val	Gly	Val	Ala	Trp	Pro	Trp	Pro	Ser	Ser	Pro	Thr	Ser	Pro

WO 00/56891

PCT/US00/07817

PF-0681 PCT

	245		250		255
Arg Thr Thr Thr	Cys Glu Leu Pro Ala	Asn Gly Gly Gly Ala	Pro		
	260	265			270
Gly Ala Arg Ser	Val Trp Thr Trp Arg	Lys Gln Ala Tyr Arg	Met		
	275	280			285
Met Leu Tyr Ser	Thr Asn Asp Cys Gln	Met Met Pro Arg Ser	Pro		
	290	295			300
Gly Ile Ser Tyr	Pro Trp Ile Tyr Phe	Val Phe Ile Leu			
	305	310			

<210> 13
 <211> 205
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4069777CD1

<400> 13	
Met Met Ser Arg Asp	Val Ile Ala Leu Val Ser Gln Val Leu Pro
1	5 10 15
Val Tyr Ser Val Phe	His Val Phe Glu Ala Ile Cys Cys Val Tyr
	20 25 30
Gly Gly Val Leu Arg	Gly Thr Gly Lys Gln Ala Phe Gly Ala Ala
	35 40 45
Val Asn Ala Ile Thr	Tyr Tyr Ile Ile Gly Leu Pro Leu Gly Ile
	50 55 60
Leu Leu Thr Phe Val	Val Arg Met Arg Ile Met Gly Leu Trp Leu
	65 70 75
Gly Met Leu Ala Cys	Val Phe Leu Ala Thr Ala Ala Phe Val Ala
	80 85 90
Tyr Thr Ala Arg Leu	Asp Trp Lys Leu Ala Ala Glu Glu Ala Lys
	95 100 105
Lys His Ser Gly Arg	Gln Gln Gln Gln Arg Ala Glu Ser Thr Ala
	110 115 120
Thr Arg Pro Gly Pro	Glu Lys Ala Val Leu Ser Ser Val Ala Thr
	125 130 135
Gly Ser Ser Pro Gly	Ile Thr Leu Thr Thr Tyr Ser Arg Ser Glu
	140 145 150
Cys His Val Asp Phe	Phe Arg Thr Pro Glu Glu Ala His Ala Leu
	155 160 165
Ser Ala Pro Thr Ser	Arg Leu Ser Val Lys Gln Leu Val Ile Arg
	170 175 180
Arg Gly Ala Ala Leu	Gly Ala Ala Ser Ala Thr Leu Met Val Gly
	185 190 195
Leu Thr Val Arg Ile	Leu Ala Thr Arg His
	200 205

<210> 14
 <211> 371
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 5309830CD1

<400> 14	
Met Ala Trp Thr Lys	Tyr Gln Leu Phe Leu Ala Gly Leu Met Leu
1	5 10 15
Val Thr Gly Ser Ile	Asn Thr Leu Ser Ala Lys Trp Ala Asp Asn
	20 25 30

WO 00/56891

PCT/US00/07817

PF-0681 PCT

	35		40		45									
Leu	Leu	Ser	Leu	Ser	Ala	Ser	His	Asn	Gln	Leu	Ser	His	Thr	Asp
	50		55		60									
Leu	Glu	Leu	His	Gln	Arg	Arg	Glu	Gln	Leu	Val	Glu	Arg	Thr	Arg
	65		70		75									
Arg	Glu	Ala	Gln	Leu	Ala	Ala	Leu	Gln	Tyr	Glu	Glu	Glu	Lys	Ile
	80		85		90									
Arg	Thr	Lys	Gln	Ile	Gln	Arg	Asp	Ala	Val	Leu	Asp	Phe	Val	Lys
	95		100		105									
Gln	Lys	Ala	Ser	Gln	Ser	Pro	Gln	Lys	Gln	His	Pro	Leu	Leu	Asp
	110		115		120									
Gly	Val	Asp	Gly	Glu	Cys	Pro	Phe	Pro	Ser	Arg	Arg	Ser	Gln	His
	125		130		135									
Thr	Asp	Asp	Ser	Ala	Leu	Cys	Met	Ser	Asp	Asp	Arg	Pro	Asn	Ala
	140		145		150									
Leu	Leu	Ser	Ser	Pro	Ala	Thr	Glu	Thr	Val	His	His	Ser	Pro	Ala
	155		160		165									
Tyr	Ser	Phe	Pro	Ala	Ala	Ile	Gln	Arg	Asn	Gln	Pro	Gln	Arg	Pro
	170		175		180									
Glu	Ser	Phe	Leu	Phe	Arg	Ala	Gly	Val	Arg	Ala	Glu	Thr	Asn	Lys
	185		190		195									
Gly	His	Ala	Ser	Pro	Leu	Pro	Pro	Ser	Ala	Ala	Pro	Thr	Thr	Asp
	200		205		210									
Ser	Thr	Asp	Ser	Ile	Thr	Gly	Gln	Asn	Ser	Arg	Gln	Arg	Glu	Glu
	215		220		225									
Glu	Leu	Glu	Leu	Ile	Asp	Gln	Leu	Arg	Lys	His	Ile	Glu	Tyr	Arg
	230		235		240									
Leu	Lys	Val	Ser	Leu	Pro	Cys	Asp	Leu	Gly	Ala	Ala	Leu	Thr	Asp
	245		250		255									
Gly	Val	Val	Leu	Cys	His	Leu	Ala	Asn	His	Val	Arg	Pro	Arg	Ser
	260		265		270									
Val	Pro	Ser	Ile	His	Val	Pro	Ser	Pro	Ala	Val	Pro	Lys	Leu	Thr
	275		280		285									
Met	Ala	Lys	Cys	Arg	Arg	Asn	Val	Glu	Asn	Phe	Leu	Glu	Ala	Cys
	290		295		300									
Arg	Lys	Ile	Gly	Val	Pro	Gln	Asp	Asn	Leu	Cys	Ser	Pro	Ser	Asp
	305		310		315									
Ile	Leu	Gln	Leu	Asn	Leu	Ser	Val	Lys	Arg	Thr	Val	Glu	Thr	Leu
	320		325		330									
Leu	Ser	Leu	Gly	Ala	His	Ser	Glu	Glu	Ser	Ser	Phe	Val	Cys	Leu
	335		340		345									
Ser	Leu	Gln	Leu	Leu	Gly	Phe	Val	Ala	Phe	Tyr	Cys	Thr	Val	Met
	350		355		360									
Leu	Thr	Leu	Cys	Val	Leu	Tyr	Tyr	Trp	Leu	Phe	Pro	Ala	Arg	
	365		370											

<210> 16

<211> 183

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 483751CD1

<400> 16

Met	Glu	Asn	Gly	Ala	Val	Tyr	Ser	Pro	Thr	Thr	Glu	Glu	Asp	Pro
1				5					10					15
Gly	Pro	Ala	Arg	Gly	Pro	Arg	Ser	Gly	Leu	Ala	Ala	Tyr	Phe	Phe
				20					25					30
Met	Gly	Arg	Leu	Pro	Leu	Leu	Arg	Arg	Val	Leu	Lys	Gly	Leu	Gln
				35					40					45

WO 00/56891

PCT/US00/07817

PF-0681 PCT

Leu	Leu	Leu	Ser	Leu	Leu	Ala	Phe	Ile	Cys	Glu	Glu	Val	Val	Ser
				50					55					60
Gln	Cys	Thr	Leu	Cys	Gly	Gly	Leu	Tyr	Phe	Phe	Glu	Phe	Val	Ser
				65					70					75
Cys	Ser	Ala	Phe	Leu	Leu	Ser	Leu	Leu	Ile	Leu	Ile	Val	Tyr	Cys
				80					85					90
Thr	Pro	Phe	Tyr	Glu	Arg	Val	Asp	Thr	Thr	Lys	Val	Lys	Ser	Ser
				95					100					105
Asp	Phe	Tyr	Ile	Thr	Leu	Gly	Thr	Gly	Cys	Val	Phe	Leu	Leu	Ala
				110					115					120
Ser	Ile	Ile	Phe	Val	Ser	Thr	His	Asp	Arg	Thr	Ser	Ala	Glu	Ile
				125					130					135
Ala	Ala	Ile	Val	Phe	Gly	Phe	Ile	Ala	Ser	Phe	Met	Phe	Leu	Leu
				140					145					150
Asp	Phe	Ile	Thr	Met	Leu	Tyr	Glu	Lys	Arg	Gln	Glu	Ser	Gln	Leu
				155					160					165
Arg	Lys	Pro	Glu	Asn	Thr	Thr	Arg	Ala	Glu	Ala	Leu	Thr	Glu	Pro
				170					175					180
Leu	Asn	Ala												

<210> 17

<211> 190

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 727332CD1

<400> 17

Met	Asp	Thr	Thr	Pro	Leu	Ile	Thr	Glu	His	Val	Ile	Asn	Thr	Thr
1				5					10					15
Gln	Asp	Pro	Cys	Ser	Trp	Val	Asp	Lys	Leu	Ser	Thr	Val	His	His
				20					25					30
Arg	Ile	Val	Gly	Cys	Ser	Leu	Ala	Val	Ile	Ser	Gly	Val	Leu	Tyr
				35					40					45
Gly	Ser	Thr	Phe	Val	Pro	Ile	Ile	Tyr	Ile	Lys	Asp	His	Ser	Lys
				50					55					60
Arg	Asn	Asp	Ser	Ile	Tyr	Ala	Gly	Ala	Ser	Gln	Tyr	Asp	Leu	Asp
				65					70					75
Tyr	Val	Phe	Ala	His	Phe	Ser	Gly	Ile	Phe	Leu	Thr	Ser	Thr	Val
				80					85					90
Tyr	Phe	Leu	Ala	Tyr	Cys	Ile	Ala	Met	Lys	Asn	Ser	Pro	Lys	Leu
				95					100					105
Tyr	Pro	Glu	Ala	Val	Leu	Pro	Gly	Phe	Leu	Ser	Gly	Val	Leu	Trp
				110					115					120
Ala	Ile	Ala	Thr	Cys	Cys	Trp	Phe	Ile	Ala	Asn	His	Ser	Leu	Ser
				125					130					135
Ala	Val	Val	Ser	Phe	Pro	Ile	Ile	Thr	Ala	Gly	Pro	Gly	Phe	Ile
				140					145					150
Ala	Ala	Met	Trp	Gly	Ile	Phe	Met	Phe	Lys	Glu	Ile	Lys	Gly	Leu
				155					160					165
Gln	Asn	Tyr	Leu	Leu	Met	Ile	Leu	Ala	Phe	Cys	Ile	Ile	Leu	Thr
				170					175					180
Gly	Ala	Leu	Cys	Thr	Ala	Phe	Ser	Lys	Ile					
				185					190					

<210> 18

<211> 361

<212> PRT

<213> Homo sapiens

WO 00/56891

PCT/US00/07817

PF-0681 PCT

<220>

<221> misc_feature

<223> Incyte ID No: 778800CD1

<400> 18

Met	Leu	Ala	Arg	Arg	Leu	Val	Trp	Ala	Leu	Ile	Ser	Glu	Ala	Thr	
1				5					10					15	
Lys	Ala	Gly	Ala	Ala	Ser	Met	Ile	His	Tyr	Met	Val	Leu	Ile	Ser	
				20					25					30	
Ala	Arg	Leu	Val	Leu	Leu	Thr	Leu	Cys	Gly	Trp	Val	Leu	Cys	Trp	
				35					40					45	
Thr	Leu	Val	Asn	Leu	Phe	Arg	Ser	His	Ser	Val	Leu	Asn	Leu	Leu	
				50					55					60	
Phe	Leu	Gly	Tyr	Pro	Phe	Gly	Val	Tyr	Val	Pro	Leu	Cys	Cys	Phe	
				65					70					75	
His	Gln	Asp	Ser	Arg	Ala	His	Leu	Leu	Leu	Thr	Asp	Tyr	Asn	Tyr	
				80					85					90	
Val	Val	Gln	His	Glu	Ala	Val	Glu	Glu	Ser	Ala	Ser	Thr	Val	Gly	
				95					100					105	
Gly	Leu	Ala	Lys	Ser	Lys	Asp	Phe	Leu	Ser	Leu	Leu	Leu	Glu	Ser	
				110					115					120	
Leu	Lys	Glu	Gln	Phe	Asn	Asn	Ala	Thr	Pro	Ile	Pro	Thr	His	Ser	
				125					130					135	
Cys	Pro	Leu	Ser	Pro	Asp	Leu	Ile	Arg	Asn	Glu	Val	Glu	Cys	Leu	
				140					145					150	
Lys	Ala	Asp	Phe	Asn	His	Arg	Ile	Lys	Glu	Val	Leu	Phe	Asn	Ser	
				155					160					165	
Leu	Phe	Ser	Ala	Tyr	Tyr	Val	Ala	Phe	Leu	Pro	Leu	Cys	Phe	Val	
				170					175					180	
Lys	Ser	Thr	Gln	Tyr	Tyr	Asp	Met	Arg	Trp	Ser	Cys	Glu	His	Leu	
				185					190					195	
Ile	Met	Val	Trp	Ile	Asn	Ala	Phe	Val	Met	Leu	Thr	Thr	Gln	Leu	
				200					205					210	
Leu	Pro	Ser	Lys	Tyr	Cys	Asp	Leu	Leu	His	Lys	Ser	Ala	Ala	His	
				215					220					225	
Leu	Gly	Lys	Trp	Gln	Lys	Leu	Glu	His	Gly	Ser	Tyr	Ser	Asn	Ala	
				230					235					240	
Pro	Gln	His	Ile	Trp	Ser	Glu	Asn	Thr	Ile	Trp	Pro	Gln	Gly	Val	
				245					250					255	
Leu	Val	Arg	His	Ser	Arg	Cys	Leu	Tyr	Arg	Ala	Met	Gly	Pro	Tyr	
				260					265					270	
Asn	Val	Ala	Val	Pro	Ser	Asp	Val	Ser	His	Ala	Arg	Phe	Tyr	Phe	
				275					280					285	
Leu	Phe	His	Arg	Pro	Leu	Arg	Leu	Leu	Asn	Leu	Leu	Ile	Leu	Ile	
				290					295					300	
Glu	Gly	Ser	Val	Val	Phe	Tyr	Gln	Leu	Tyr	Ser	Leu	Leu	Arg	Ser	
				305					310					315	
Glu	Lys	Trp	Asn	His	Thr	Leu	Ser	Met	Ala	Leu	Ile	Leu	Phe	Cys	
				320					325					330	
Asn	Tyr	Tyr	Val	Leu	Phe	Lys	Leu	Leu	Arg	Asp	Arg	Ile	Val	Leu	
				335					340					345	
Gly	Arg	Ala	Tyr	Ser	Tyr	Pro	Leu	Asn	Ser	Tyr	Glu	Leu	Lys	Thr	
				350					355					360	

Asn

<210> 19

<211> 97

<212> PRT

<213> Homo sapiens

<220>

WO 00/56891

PCT/US00/07817

PF-0681 PCT

Lys	Val	Phe	Glu	Ser	Ile	Asn	Met	Asp	Thr	Asn	Asp	Met	Trp	Leu
				110					115					120
Met	Met	Arg	Lys	Ala	Tyr	Lys	Tyr	Ala	Phe	Asp	Lys	Tyr	Arg	Asp
				125					130					135
Gln	Tyr	Asn	Trp	Phe	Phe	Leu	Ala	Arg	Pro	Thr	Thr	Phe	Ala	Ile
				140					145					150
Ile	Glu	Asn	Leu	Lys	Tyr	Phe	Leu	Leu	Lys	Lys	Asp	Pro	Ser	Gln
				155					160					165
Pro	Phe	Tyr	Leu	Gly	His	Thr	Ile	Lys	Ser	Gly	Asp	Leu	Glu	Tyr
				170					175					180
Val	Gly	Met	Glu	Gly	Gly	Ile	Val	Leu	Ser	Val	Glu	Ser	Met	Lys
				185					190					195
Arg	Leu	Asn	Ser	Leu	Leu	Asn	Ile	Pro	Glu	Lys	Cys	Pro	Glu	Gln
				200					205					210
Gly	Gly	Met	Ile	Trp	Lys	Ile	Ser	Glu	Asp	Lys	Gln	Leu	Ala	Val
				215					220					225
Cys	Leu	Lys	Tyr	Ala	Gly	Val	Phe	Ala	Glu	Asn	Ala	Glu	Asp	Ala
				230					235					240
Asp	Gly	Lys	Asp	Val	Phe	Asn	Thr	Lys	Ser	Val	Gly	Leu	Ser	Ile
				245					250					255
Lys	Glu	Ala	Met	Thr	Tyr	His	Pro	Asn	Gln	Val	Val	Glu	Gly	Cys
				260					265					270
Cys	Ser	Asp	Met	Ala	Val	Thr	Phe	Asn	Gly	Leu	Thr	Pro	Asn	Gln
				275					280					285
Met	His	Val	Met	Met	Tyr	Gly	Val	Tyr	Arg	Leu	Arg	Ala	Phe	Gly
				290					295					300
His	Ile	Phe	Asn	Asp	Ala	Leu	Val	Phe	Leu	Pro	Pro	Asn	Gly	Ser
				305					310					315

Asp Asn Asp

<210> 25

<211> 326

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2506558CD1

<400> 25

Met	Glu	Phe	Leu	Trp	Asp	Phe	Leu	Asn	His	Gln	Glu	Gly	Pro	Arg
1				5					10					15
Ile	Arg	Asp	His	Leu	Ser	His	Gly	Glu	Ile	Asn	Leu	His	Glu	Phe
				20					25					30
Ser	Lys	Glu	Thr	Thr	Asn	Gln	Leu	Leu	Ala	Phe	Ser	Leu	Val	Leu
				35					40					45
Leu	Leu	Arg	Phe	Val	Asp	Asp	Cys	Leu	Leu	Ser	Val	Phe	Lys	Glu
				50					55					60
Lys	Ser	Ala	Val	Glu	Leu	Leu	Ile	Ser	Leu	Ala	Glu	Gly	Tyr	Ser
				65					70					75
Ser	Arg	Cys	His	Pro	Val	Phe	Gln	Leu	Lys	Lys	Gln	Val	Leu	Ser
				80					85					90
Cys	Glu	Glu	Ser	Ile	Arg	Val	Trp	Ala	Leu	Leu	Pro	Phe	Pro	Glu
				95					100					105
Glu	Leu	Thr	Arg	Gln	Ala	Val	Arg	Leu	Glu	Asp	Asn	Ser	Glu	Thr
				110					115					120
Asn	Ala	Cys	His	Ser	Leu	Ile	Thr	Lys	Met	Thr	Asp	Glu	Leu	Tyr
				125					130					135
His	His	Met	Pro	Glu	Asn	Arg	Cys	Val	Leu	Lys	Asp	Leu	Asp	Arg
				140					145					150
Leu	Pro	Thr	Glu	Thr	Trp	Pro	Gln	Leu	Leu	Arg	Glu	Leu	Cys	Ser

WO 00/56891

PCT/US00/07817

PF-0681 PCT

Thr	Pro	Val	Pro	155	Thr	Leu	Phe	Cys	Pro	160	Arg	Ile	Val	Leu	Glu	Val	165
				170						175							180
Leu	Val	Val	Leu	Arg	Ser	Ile	Gly	Glu	Gln	Cys	Arg	Arg	Val	Ser			185
				185						190							195
Ser	Gln	Val	Thr	Val	Ala	Ser	Glu	Leu	Arg	His	Arg	Gln	Trp	Val			200
				200						205							210
Glu	Arg	Thr	Leu	Arg	Ser	Arg	Gln	Arg	Gln	Asn	Tyr	Leu	Arg	Met			215
				215						220							225
Trp	Ser	Ser	Ile	Arg	Leu	Leu	Ser	Pro	Val	Leu	Ser	Leu	Ile	Leu			230
				230						235							240
Leu	Leu	Ile	Ala	Leu	Glu	Leu	Val	Asn	Ile	His	Ala	Val	Cys	Gly			245
				245						250							255
Lys	Asn	Ala	His	Glu	Tyr	Gln	Gln	Tyr	Leu	Lys	Phe	Val	Lys	Ser			260
				260						265							270
Ile	Leu	Gln	Tyr	Thr	Glu	Asn	Leu	Val	Ala	Tyr	Thr	Ser	Tyr	Glu			275
				275						280							285
Lys	Asn	Lys	Trp	Asn	Glu	Thr	Ile	Asn	Leu	Thr	His	Thr	Ala	Leu			290
				290						295							300
Leu	Lys	Met	Trp	Thr	Phe	Ser	Glu	Lys	Lys	Gln	Met	Leu	Ile	His			305
				305						310							315
Leu	Ala	Lys	Lys	Ser	Thr	Ser	Lys	Val	Leu	Leu							320
				320						325							

<210> 26

<211> 247

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2546025CD1

<400> 26

Met	Leu	Arg	Phe	Ile	Gln	Lys	Phe	Ser	Gln	Ala	Ser	Ser	Lys	Ile			
1				5					10					15			
Leu	Lys	Tyr	Ser	Phe	Pro	Val	Gly	Leu	Arg	Thr	Ser	Arg	Thr	Asp			
				20					25					30			
Ile	Leu	Ser	Leu	Lys	Met	Ser	Leu	Gln	Gln	Asn	Phe	Ser	Pro	Cys			
				35					40					45			
Pro	Arg	Pro	Trp	Leu	Ser	Ser	Ser	Phe	Pro	Ala	Tyr	Met	Ser	Lys			
				50					55					60			
Thr	Gln	Cys	Tyr	His	Thr	Ser	Pro	Cys	Ser	Phe	Lys	Lys	Gln	Gln			
				65					70					75			
Lys	Gln	Ala	Leu	Leu	Ala	Arg	Pro	Ser	Ser	Thr	Ile	Thr	Tyr	Leu			
				80					85					90			
Thr	Asp	Ser	Pro	Lys	Pro	Ala	Leu	Cys	Val	Thr	Leu	Ala	Gly	Leu			
				95					100					105			
Ile	Pro	Phe	Val	Ala	Pro	Pro	Leu	Val	Met	Leu	Met	Thr	Lys	Thr			
				110					115					120			
Tyr	Ile	Pro	Ile	Leu	Ala	Phe	Thr	Gln	Met	Ala	Tyr	Gly	Ala	Ser			
				125					130					135			
Phe	Leu	Ser	Phe	Leu	Gly	Gly	Ile	Arg	Trp	Gly	Phe	Ala	Leu	Pro			
				140					145					150			
Glu	Gly	Ser	Pro	Ala	Lys	Pro	Asp	Tyr	Leu	Asn	Leu	Ala	Ser	Ser			
				155					160					165			
Ala	Ala	Pro	Leu	Phe	Phe	Ser	Trp	Phe	Ala	Phe	Leu	Ile	Ser	Glu			
				170					175					180			
Arg	Leu	Ser	Glu	Ala	Ile	Val	Thr	Val	Ile	Met	Gly	Met	Gly	Val			
				185					190					195			
Ala	Phe	His	Leu	Glu	Leu	Phe	Leu	Leu	Pro	His	Tyr	Pro	Asn	Trp			
				200					205					210			

WO 00/56891

PCT/US00/07817

PF-0681 PCT

Phe	Lys	Ala	Leu	Arg	Ile	Val	Val	Thr	Leu	Leu	Ala	Thr	Phe	Ser
				215					220					225
Phe	Ile	Ile	Thr	Leu	Val	Val	Lys	Ser	Ser	Phe	Pro	Glu	Lys	Gly
				230					235					240
His	Lys	Arg	Pro	Gly	Gln	Val								
				245										

<210> 27

<211> 278

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3145660CD1

<400> 27

Met	Ala	Tyr	Phe	Tyr	Met	Cys	Asp	Arg	Ala	Asn	Leu	Phe	Met	Lys
1				5					10					15
Glu	Asn	Lys	Phe	Tyr	Thr	His	Ser	Ser	Phe	Phe	Ile	Pro	Ile	Ile
				20					25					30
Tyr	Ile	Leu	Val	Leu	Gly	Val	Phe	Tyr	Asn	Glu	Asn	Thr	Lys	Glu
				35					40					45
Thr	Lys	Val	Leu	Asn	Arg	Glu	Gln	Thr	Asp	Glu	Trp	Lys	Gly	Trp
				50					55					60
Met	Gln	Leu	Val	Ile	Leu	Ile	Tyr	His	Ile	Ser	Gly	Ala	Ser	Thr
				65					70					75
Phe	Leu	Pro	Val	Tyr	Met	His	Ile	Arg	Val	Leu	Val	Ala	Ala	Tyr
				80					85					90
Leu	Phe	Gln	Thr	Gly	Tyr	Gly	His	Phe	Ser	Tyr	Phe	Trp	Ile	Lys
				95					100					105
Gly	Asp	Phe	Gly	Ile	Tyr	Arg	Val	Cys	Gln	Val	Leu	Phe	Arg	Leu
				110					115					120
Asn	Phe	Leu	Val	Val	Val	Leu	Cys	Ile	Val	Met	Asp	Arg	Pro	Tyr
				125					130					135
Gln	Phe	Tyr	Tyr	Phe	Val	Pro	Leu	Val	Thr	Val	Trp	Phe	Met	Val
				140					145					150
Ile	Tyr	Val	Thr	Leu	Ala	Leu	Trp	Pro	Gln	Ile	Ile	Gln	Lys	Lys
				155					160					165
Ala	Asn	Gly	Asn	Cys	Phe	Trp	His	Phe	Gly	Leu	Leu	Leu	Lys	Leu
				170					175					180
Gly	Phe	Leu	Leu	Leu	Phe	Ile	Cys	Phe	Leu	Ala	Tyr	Ser	Gln	Gly
				185					190					195
Ala	Phe	Glu	Lys	Ile	Phe	Ser	Leu	Trp	Pro	Leu	Ser	Lys	Cys	Phe
				200					205					210
Glu	Leu	Lys	Gly	Asn	Val	Tyr	Glu	Trp	Trp	Phe	Arg	Trp	Arg	Leu
				215					220					225
Asp	Arg	Tyr	Val	Val	Phe	His	Gly	Met	Leu	Phe	Ala	Phe	Ile	Tyr
				230					235					240
Leu	Ala	Leu	Gln	Lys	Arg	Gln	Ile	Leu	Ser	Glu	Gly	Lys	Gly	Glu
				245					250					255
Pro	Leu	Phe	Ser	Asn	Lys	Ile	Ser	Asn	Phe	Leu	Leu	Val	Ile	Ser
				260					265					270
Val	Val	Ser	Phe	Leu	Gly	Lys	Phe							
				275										

<210> 28

<211> 320

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

WO 00/56891

PCT/US00/07817

PF-0681 PCT

Lys	Lys	Lys	Gly	Leu	Leu	Arg	Leu	Ala	Arg	Lys	Gly	Ser	Met	Arg
				35					40					45
Ala	Gly	Gln	Gly	Gly	His	Ala	Tyr	Leu	Lys	Glu	Trp	Leu	Trp	Trp
				50					55					60
Ala	Gly	Leu	Leu	Ser	Met	Gly	Ala	Gly	Glu	Val	Ala	Asn	Phe	Ala
				65					70					75
Ala	Tyr	Ala	Phe	Ala	Pro	Ala	Thr	Leu	Val	Thr	Pro	Leu	Gly	Ala
				80					85					90
Leu	Ser	Val	Leu	Val	Ser	Ala	Ile	Leu	Ser	Ser	Tyr	Phe	Leu	Asn
				95					100					105
Glu	Arg	Leu	Asn	Leu	His	Gly	Lys	Ile	Gly	Cys	Leu	Leu	Ser	Ile
				110					115					120
Leu	Gly	Ser	Thr	Val	Met	Val	Ile	His	Ala	Pro	Lys	Glu	Glu	Glu
				125					130					135
Ile	Glu	Thr	Leu	Asn	Glu	Met	Ser	His	Lys	Leu	Gly	Asp	Pro	Gly
				140					145					150
Phe	Val	Val	Phe	Ala	Thr	Leu	Val	Val	Ile	Val	Ala	Leu	Ile	Leu
				155					160					165
Ile	Phe	Val	Val	Gly	Pro	Arg	His	Gly	Gln	Thr	Asn	Ile	Leu	Val
				170					175					180
Tyr	Ile	Thr	Ile	Cys	Ser	Val	Ile	Gly	Ala	Phe	Ser	Val	Ser	Cys
				185					190					195
Val	Lys	Gly	Leu	Gly	Ile	Ala	Ile	Lys	Glu	Leu	Phe	Ala	Gly	Lys
				200					205					210
Pro	Val	Leu	Arg	His	Pro	Leu	Ala	Trp	Ile	Leu	Leu	Leu	Ser	Leu
				215					220					225
Ile	Val	Cys	Val	Ser	Thr	Gln	Ile	Asn	Tyr	Leu	Asn	Arg	Ala	Leu
				230					235					240
Asp	Ile	Phe	Asn	Thr	Ser	Ile	Val	Thr	Pro	Ile	Tyr	Tyr	Val	Phe
				245					250					255
Phe	Thr	Thr	Ser	Val	Leu	Thr	Cys	Ser	Ala	Ile	Leu	Phe	Lys	Glu
				260					265					270
Trp	Gln	Asp	Met	Pro	Val	Asp	Asp	Val	Ile	Gly	Thr	Leu	Ser	Gly
				275					280					285
Phe	Phe	Thr	Ile	Ile	Val	Gly	Ile	Phe	Leu	Leu	His	Ala	Phe	Lys
				290					295					300
Asp	Val	Ser	Phe	Ser	Leu	Ala	Ser	Leu	Pro	Val	Ser	Phe	Arg	Lys
				305					310					315
Asp	Glu	Lys	Ala	Met	Asn	Gly	Asn	Leu	Ser	Asn	Met	Tyr	Glu	Val
				320					325					330
Leu	Asn	Asn	Asn	Glu	Glu	Ser	Leu	Thr	Cys	Gly	Ile	Glu	Gln	His
				335					340					345
Thr	Gly	Glu	Asn	Val	Ser	Arg	Arg	Asn	Gly	Asn	Leu	Thr	Ala	Phe
				350					355					360

<210> 30

<211> 1716

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1316927CB1

<400> 30

ccccgactct	ggctgggctg	aggagggggc	cccacaggcc	tgggtggaag	ccgatccctg	60
agcaatcccc	ctgtgcagga	ttgaacatga	ttgtctctct	ttttctcctt	tttctgactt	120
taaggcaact	ttgtccctaa	caaaatgtgg	aagggattag	tcaagaggaa	tgcattctgtg	180
gaaacagttg	ataataaaaac	gtctgaggat	gtaaccatgg	cagcagcttc	tcctgtcaca	240
ttgaccaaag	ggacttcggc	agcccacctc	aactctatgg	aagtcacaac	agaggacaca	300
agcaggacag	atgtgagtga	accagcaact	tcaggagggtg	cagctgatgg	tgtgacctcc	360

WO 00/56891

PCT/US00/07817

PF-0681 PCT

```

attgtctccca cggtgtgtggc ctccagtagc actgcggcct ccattacgac tgcggcctcc 420
agtatgactg tggcctccag tgctccacg actgcagcct ccagtacaac tgtggcctcc 480
attgtctccca cgactgcagc ctccagtagc actgcggcct ccagcactcc catgacactt 540
gcaactcccc cgcccacgtc cacttccaca gggcgggacc cgctccactac cgccactggg 600
catccatctc tcagcacagc cctcgcacaa gtgccaaaga gcagcgcgtt gccaaagaaca 660
gcaaccctgg ccacattggc cacacgtgct cagactgtag cgaccacagc aaacacaagc 720
agccccatga gcaactcgtc aagtccttcc aagcacatgc ccagtacac cgcggaagc 780
cctgtacccc ctatgcgtcc ccaagcacaa ggtcccatta gccaggtgtc agtggaccag 840
cctgtgggta acacaacaaa taaatccaca ccatgcccct caaacacaa cccagagccc 900
gccccacccc ccacagtggg gaccaccacc aaggcacaag ccagggagcc aactgccagc 960
ccagtgccag tacctcacac cagcccaatc cctgagatgg aggccatgtc cccacagaca 1020
cagccaagcc catgcccata taccagagg gccgtggggc caggcacatc ccaggcaccg 1080
gagcaggtag agactgaagc cacaccaggt actgattcca ctgggccaac acccaggagc 1140
tcagggggca ctaagatgcc agccacggac tcgtgccagc ccagcaccca aggccagtag 1200
atgggtggta ccaactgagcc cctcaccag gccgtggtag acaaaactct ccttctgggtg 1260
gtgctgttac tcgggggtgac ccttttcata acagtcttgg ttttgtttgc cctgcaggcc 1320
tatgagagct acaagaagaa ggactacacc caggtggact acttaatcaa cgggatgtat 1380
gcggaactcag aaatgtgagg ggggcggggg cctggcgga ggctggccc ctctctcgtc 1440
ctttcctttt gcctttgaga ccaaaccaag tgcttccaaa ttcttttggg gcaattgagg 1500
agatatgcca gatgcttaaa cacatttaat tgctgtcaga ttaattccat gatcactaaa 1560
gagttgctgc ttttttcata tttatttttg taaatgattc tgtgccagg agcagctggg 1620
ggttccacct cagggtgggg cgggcaggac cccgtctccc caggtgtcgg agcctgacct 1680
gaattaaagt actgactgct cgccaaaaaa aaaaaa 1716

```

<210> 31
 <211> 1133
 <212> DNA
 <213> Homo sapiens

<220>
 <221> unsure
 <222> 1094
 <223> a or g or c or t, unknown, or other

<220>
 <221> misc_feature
 <223> Incyte ID No: 1354891CB1

```

caggtaggca agtgagcact gcagccaatg ccaactgtatc ccttgcaggt attctggatg 60
gtgaaatgga ccccaaagggt atgtgttcc cactgctgtg ggtactgaat gccaaagaat 120
ttctgggctg gtgttgggat tgtgtgcagg ttcaggagc aggaactcctt cccacctgct 180
tctgcttcc gtctgcctt actggctctt tctccaaact tcccatcacc agtctttctc 240
tttcaagtac ctgctattga ggagaacttg ctgatgaca agcatttgc gaagccatgg 300
gatgctaaga agctatcctc atcctcttcc cgacctcggt cctgtgaagt ccttggatt 360
aacatctttc catctcctga ccagcctgcc aatgtgectg tcctccacc tgccatgaac 420
acgggggggt cctacactga cctcaccaac ctgcacttcc cccaccact gccaccccc 480
ctggaccctg aagagacagc ctaccctagc ctgagtgagg gcaacagtac ctccaattg 540
accacacca tgactcacct gggcatcagc aggggcattg gcctgggccc aggtatgat 600
gcaccaggac ttcattcacc tctcagccac ccatecctgc agtccctcc aagcaatccc 660
aacctccagg ctctccctgag cagtccctag cccagcttc agggctccca cagccacccc 720
tctctgctg cctcctcctt ggcccgcct gtactgccc ccacctccct gggccacccc 780
tcaactcagt cctcggctct cctctctcc tcttgcctc cctccacttc atctcctgtt 840
ttgggcgcgc cctcttacc tgctctacc cctggggcct cccccacca ccgcctgtgt 900
cccctcagcc cctgagttt gctcgcgggc ccagccgagc ccagaaggtc ccaacagcag 960
ctgcccacac agttttcgcc aacaatgtca cccacctgt cttccatcac tcagggcgct 1020
ccctggatag cagtaaaactg tccactgacc agcgggttaac cccataccca tacagctccc 1080
caagtctggt tctncttacc cagggccaca ccccaaagtc tctacagcag cca 1133

```

<210> 32
 <211> 3324

WO 00/56891

PCT/US00/07817

PF-0681 PCT

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1415487CB1

<400> 32

```

tagatgacaa tagtgtatatt atgctgtacc ttttctatgt ttagatgtgt gtagatgcac 60
aaatacttgc cgtgggtgta agattgcctg cagtattcac accataacat gcactgcagg 120
cttgtagcct aggagcagtc gactctagcg tccatcctgg gtgtgtattg ggctgtacca 180
tctgggttgg tgtaagtgca cgctacaatg ttcctatggg cataaaatca cctaacgaca 240
catttctaac gacacgtccc tgtcgttaag caatgcatga ctgtactaac ctctcctgca 300
gttgctcaga tggggcgagc ctactgtttg tgctagggcc ctggctgcta ggctggaagc 360
tcatacgtct cagtgcctct tcacctccca agctggtttg atgcccacaa acgtttggct 420
ggagaccctt gaagtctctg ctaccatcca agctggtttg gagacgtgaa ccagaccaat 480
gaagggtctg ctgtacaatg attctctctg cctattttat taacttcac taccttgcca 540
agagcacaaa aaaaaccatg ctaactttaa ctttgggtat tgcaatlaca ttctccttgg 600
tttgacgtgg aacatttttt ccatatagct ccaatcctgc taatccgaag ccaaagagag 660
tgtttcttca gcatatgact agaacattcc atgacttggg aggaaatgca gttaaacggg 720
actctggaat atggatcaat gggtttgatt atactggaat ttctcacata accctcaca 780
ttcctgagat caatgatagt atccgagctc actgtgagga gaatgcacct ctttgtgggt 840
ttccttggtg tcttccagtg cactttctga tcaggaaaaa ctggtatctt cctgccccag 900
aagtttctcc aagaaatcct cctcatttcc gactcatatc caaagaacag acacettggg 960
attctataaa attgactttt gaagcaacag gaccaagcca tatgtccttc tatgtctcag 1020
cccacaaagg gtcaacactt tctcagtggt tctctggcaa tggcacccca gtcacaagta 1080
aaggaggaga ctactttgtc ttttactccc atggactcca ggctctgca tggcagttct 1140
ggatagaagt gcaggtttca gaagaacatc ctgaaggaa ggtaaccgtg gccattgctg 1200
cccactatct gtctggggaa gacaagagat cccctcaact ggatgctctg aaggaaaagt 1260
tcccagattg gacatttccc tctgcctggg tgtgcacctg cgatctcttt gtattttaat 1320
cttgtggatg agctctaagt acatgcccag tggatactcc atgaaattta atgatcatat gttcaaagag 1440
atgttacgtg gatgtttgta acgttaagtca atgaatttta gtttagctgt ggcgcagtga 1500
ctttctgggt ttacgctttt gaaatgcca gtcttttggc acttcagcac atgtgggtac 1560
tgccactaca cacacgtcat tttatatgac ctttaaggaca aagccaacaa tccacttcaa 1620
tagctgcccc tttaggatca agaaagatgt acactgtcag agcattgtta atgagacaaa 1680
agttgtttcc aatttaagcc ccaaaaccat ttgttgatt agtggaatgg gggtaaaata 1740
tcattcactg aggtaatgat tccccttgag aatalaactc tgtgtaggtc actggaaagt 1800
gattgccata gggctgggag agaagcattg cactcttgag gctgtagcct gtgtcaagct 1860
gtttcttcag gcagcctctc aaatgtgctt tgtctctctg tgctgaggcc tggaccctgt 1920
gctgagctgg tgactcactg tcttgacaag tggacacaca gatgcaactg tgtgctgctt 1980
tcttgagggt gttttctatg cctgttttcc tctgaaacat gtctgttacc cctctccatc 2040
ttaccaagtt gaaaagggga atatttggcc acataccctt ctgggttttc taggttcttt 2100
tggttcagaa tattgtttgt gccagtacat gaccttaact tcttctctca gagcactgag 2160
ctgccatctg ggctattctg gggtagaagg aaggctggga gtgggtggga ttttataaat 2220
atltattctc ttttctttgt ttcataggag tcttgtgtta tacaagggtt gtccttcatg 2280
gtataatctt actgatgcac atccagcaga ctggctttcc tgagacttga ggttgtggct 2400
gtttttctca gtaacttact gtacgtgtag gtgggtcaga tctgcgttaa tggcagcatg 2460
tatactggaa tgagaccact catlttgaag atggctatgt agcttgtaag gtgtatcaca 2520
aggacttaaa aggtgggttt ttgggtccag cagtgggggc attgggtgaga tcaatggtaa 2580
gcagtacctc tcatggcttt atcattagga aatgtgaaac gttggacaaa ttttgagttt 2640
actgtgcaag ctttcttttt aagaaaaggc acagttaaca aaaaagggtg gctagattta 2700
taacaaggac aaaaagttga gagagaggaa tgctcttgaa aggtgggtctg tggatctgtc 2760
tcttgggtga tggaggaaat agtatgcatt gccggagaaa acgtccttga agctgcttgt 2820
tgaatagaaa gagcacagta tttaaatcat gccctcggtt gcctgcctaa tctgtgactc 2880
ctcatgtgta tgatgtgctt atgtagatgg ggctgcaacc agagctgaat aacatgttag 2940
cctaaaaact aactgggccc tgcacactgg aatcattgct ctctacttt tatctgtcag gtagcacata 3060
gctcacacat gtgcttcaag agtctggctc tcactgttgt ggagaaaaag taataatttc 3120
tcaatgaatt ttaaaaatgg gccatttttc tatccccgtg gtccatctga tataattagt 3180

```

WO 00/56891

PCT/US00/07817

PF-0681 PCT

gttccctgtg aattcccccc ctctatggga aggatgcctt tactctttat cagtaataaa 3240
ttatgactgt ttatcatattg ccttaggggtt atttccccgg gtgaaaccat tggcttttgt 3300
gttgggtttc cttagcataa gaag 3324

<210> 33
<211> 1023
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1693184CB1

<400> 33
tggcgaggaaag tggcgagagcg cgacgggtgcg gggcgcgcgcg ggcacggggcc agcggggatgg 60
gagcaggggtc ccccggcggc ccgcagcctc gggagcccgcg ctgaagccgg gggcgggacc 120
agcgcgagcg cgacatgtgt ctgcgcctcg gaggcctgag tgtgggagac ttccggaagg 180
tgctgatgaa gacaggcctg gtgctgggtgg tgcctgggcca tgtgagcttc atcacagctg 240
ccctgttcca tggcacagtg ctgcgctacg tgggcacccc tcaagatgag gtggctctgc 300
agtactgctt ggtcaacatc ctctctgtca ctcccgccat cgtgggtcgc acttcaggca 360
tcgcagccat cgtgttgtca cgctacctcc ctagcacccc cctgcgctgg acagtgttta 420
gctcgagcgt ggctgtgtgt ctccctttctc tgacctgtgc cctcgccctc ttggcctcca 480
tcgccatgac ctttgcacc cagggcaagg cactgctggc tgcctgcaat tttgggagct 540
ctgaactact ggccctcgca cctgactgtc ccttcgaccc cacacgcatt tatagctcca 600
gcctgtgctt ctggggcacc gccctagtgc tctgctgtgg ggagaacgtg tttgctgtac 660
gctgtgctca gctcaccac cagctgctgg agctgagggc ctgggtggggg aaaagcagcc 720
accacatgat gcgggagaac ccagagctgg tggagggccg tgacctgtgc agctgcacca 780
gctctgagcc tctgacctc tgagagatga tgcctgccc agggccgatg gccactagga 840
ccctgcaagg aactctgctc tgtgaccagg ccaggattcc tggagctggc ctgagagggc 900
tcaatggacc ctcggggacc caagtggggc tttcaaccct ctccccacc acccagccca 960
ctgcactgaa atgagacttt attctgaaat tattaaaaag aacagagatg ctcaaaaaaa 1020
aaa 1023

<210> 34
<211> 2091
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1695049CB1

<400> 34
tgaagccgca gccgcccggc taggcccccg gcggtctctag cccagggcgcg cccgcggggc 60
gctgggcctg gctcccggct ccggtttccg ggcggcgcg gggccgctca ccatgcccgg 120
caagcaccag catttccagg aacctgaggt cggctgctgc gggaaatact tctgttttgg 180
cttcaacatt gtcttcttgg tgctgggagc cctgttctcg gctatcggcc tctgggcctg 240
gggtgagaag ggcgttctct cgaacatctc agcgtgaca gatctgggag gccttgacct 300
cgtgtggctg tttgtggtag ttggaggcgt catgtcgggt ctgggctttg ctggctgcat 360
tggggccctc cgggagaaca ccttctctgt caagttttcc tccgtgttcc tccgtctcat 420
cttcttctcg gagctggcaa cagggatcct ggcctttgtc ttcaaggact ggattcgaga 480
ccagctcaac ctcttcatca acaacaacgt caaggcctac cgggacgaca ttgacctcca 540
gaacctcatt gactttgtct aggaatactg gtcttctgctc ggagcccgag gcccacatga 600
ctggaacctc aatatctact tcaactgcac tgacttgaac cccagccggg agcgtgcgg 660
gggtgccctt tctgtctgct tcagggaccc tgcggaggat gtcctcaaca cccagtgtgg 720
ctacgacgtc cggctcaaac tggagctgga gcagcagggc ttcacccaca ccaaaggctg 780
cgtgggcccag tttgagaagt ggctgcagga caacctgatt gtggtggcgg gactcttcat 840
gggcatgcgc ctctctcaga tctttggcat gtcctggcc cagaacctcg tgagtgcacat 900
caaggcagtg aaagccaact ggagcaaatg gaatgatgac tttgaaaacc actggcttac 960
gcccaaccatt tccgaggtcc tgtccacggc ggggcctcag cagaactctc tgactggggc 1020
ccctggcccc gccccaccca gccgacatgt tttctttggc ctgggtgggt tataccctga 1080

WO 00/56891

PCT/US00/07817

PF-0681 PCT

gccaaccttt	aaaaattggt	agatttcaca	taaaagtcca	gatccacage	ttctcttgaa	1140
gaatgaccac	ctggctacgc	cggtctctcg	gtggcaaacac	tacctgggac	actgcctccc	1200
cagtcaccaa	gggccccagc	tggccccgtc	tactcaccta	agtgcgcgct	gagccttgta	1260
caactaggagc	tggcctccca	cctctgcagg	gttatttctt	gcacctcgag	gccgctgcgg	1320
gccaatctgg	agtgaaacac	ggggacctga	aggatggaga	ggctggaccc	cgctttgaag	1380
aggggtgcagc	ctgggaaggg	cggccttgc	ggggactgcg	gtgggagtag	agtgcacagg	1440
agaggggtctg	aggggtggga	tgggggtcag	gacaattttg	caaaagaagt	agctggaagc	1500
catgggactg	gcgggagcct	gtttggggga	tctggatgg	tgactcctag	gagtcaagtt	1560
cagcatcttc	gccgtggctg	cagagctgcc	tgatgggcac	tagagggcac	gccagcccca	1620
cactccctgg	gtctggcttc	ctcccgcaac	ctcactctag	tagagcctgt	gcctgcctac	1680
tagcgtctcg	gggttcggag	agtttgggaa	tttctcagag	ccaactggct	caggcttggg	1740
aaggctggct	gctgccctca	gctccgcctc	atcagctatg	tgaaggggtg	tgtgtggagt	1800
gacctgcgcg	ccccctccct	gggctgggtc	agagatctca	aactccgatg	ccccgggggc	1860
cacgtatgtt	gtgtaaatgg	atgaaacagg	cccttgagtt	gggagcctgc	ttcactttga	1920
ctttcccact	gttgctggag	acaaagacat	cgtgatgaga	gaaagtctcg	acaatctagt	1980
cggtaacagc	cactttccct	gagaccaaga	gagtgccggt	gggatggggg	ggagagcagg	2040
gtcccgctcg	acaatggcgg	ctgccataat	ccagtgtagc	taatggctct	g	2091

<210> 35

<211> 2888

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1802448CB1

<400> 35

ccggaggagg	tgagcgccag	gtcgccttcg	cgccccgggg	acacaggcag	ggacgcggga	60
gctgatgcgg	ctggaccggc	cggggaaaca	gtattttctg	gaagggggcc	cctctgaagc	120
ggtccaggat	cctgcacatg	gcgctgaccg	gggcctcaga	ccccctcgca	gaggcagagg	180
ccaaacggga	gaagcccttt	ctgctgcggg	cattgcagat	cgcgctgggtg	gtctccctct	240
actgggtcac	ctccatctcc	atgggtgttc	ttaataagta	cctgctggac	agccccctcc	300
tgcggtcgga	cacccccatc	tctgtcacct	tctaccagtg	cctggtgacc	acgtgctgtg	360
gcaaaggcct	cagcgctctg	gccgcctgct	gccctgggtg	cgtggacttc	cccagcttgc	420
gcttgacact	caggggtggc	cgcagcgctc	tgccccgtgc	ggtgggtcttc	atcgccatga	480
tcaccttcaa	taacctctgc	ctcaagtagc	tgggtgtggc	cttctacaat	gtgggcccgt	540
cactcaccac	cgtcttcaac	gtgctgctct	cctacctgct	gctcaagcag	accacctcct	600
tctatgccct	gctcacctgc	ggtatcatca	tccggggcct	ctggcttggg	gtggaccagg	660
agggggcaga	aggcaccctg	tctgtggctg	gcacctctct	cggcgtgctg	gctagcctct	720
glgtctcgct	caacgccatc	tacaccacga	aggtgctccc	ggcggtggag	ggcagcatct	780
ggcgctcgag	tttctacaac	aacgtcaacg	cctgcctcct	cttctgccc	ctgctcctgc	840
tgctcgggga	gcttcaggcc	ctgctgactc	ttgcccagct	gggcagtgcc	cacttctggg	900
ggatgatgac	gctgggcggc	ctggttggct	ttgccatcgg	ctacgtgaca	ggactgcaga	960
tcaagttcac	cagtccgctg	accacacaat	tgctggggc	ggccaaggcc	tgtgccaga	1020
cagtgtctgg	cgtgctctac	tacgaggaga	ccaagagctt	cctctggtgg	acgagcaaca	1080
tgatggtgct	gggcggctcc	tccgcctaca	cctgggtcag	gggctgggag	atgaagaaga	1140
ctccggagga	gcccagcccc	aaagacagcg	agaagagcgc	catgggggtg	tgagcaccac	1200
aggcaccctg	gatggcccg	ccccggggcc	cgtacacagg	cagggccagc	acagttagta	1260
aggcggtctc	ctggacccca	gaagcgtgct	gtgggtgtga	ctgggtgcta	cttatagacc	1320
caatcagaat	acggtggttg	agaaggaacc	agtgtttaca	agtaatatca	gaaagttaga	1380
ggaaccagtg	tttacaagta	ataccagaaa	gttgccaaac	ccttctctat	cctctcgtat	1440
ttctgagttt	ttgtccttcc	cgagggagca	ccctagttag	agttgaaccc	cttctctctg	1500
cctccagggc	ctgtctgcct	ccacatcact	ctgaggacag	ggacaggcaa	caaccttgaa	1560
gggacagcaa	tggcaaagcc	acaaaggett	cactgtactc	aggggagatg	gccctaccac	1620
agccacctgg	agaggggttg	gaagccttcc	gtctgcgggtg	ggcaggcagc	ctcaccttgg	1680
gcccacagac	cggccttcc	ttggaggaaa	gtgtggcctg	gactgaggya	ggaaatggag	1740
gagttccctc	tgacaccagc	agatccccag	gggctgctgg	gcagtggcct	gggaatgggg	1800
tggattgtga	gaaagtgtct	accatctata	cacctgttat	gtccagcttt	tgaacacaag	1860
ggaaccatgc	ttctcttaga	ggttaagcag	ggtcattaac	atcctcccc	agtccttaac	1920
atcacattgt	cctgcgtggc	tctcttgccc	ctgagtggca	cctgtccctc	tgggtctccca	1980

WO 00/56891

PCT/US00/07817

PF-0681 PCT

```
gcacctggcc caggtaacag ccttctgaaa gcagagccaa ggagctgctt ctctcttctc 2040
ccagttctac ctccccagaa gccttctctc ccaggtgggg ctgatggagc aagggtccag 2100
actaggagcc ttccacccca gctgtgtctg gcgcccctag atctctgcaa gggaggtgtt 2160
acagctgggt ctgagccgct tgccttgtga tggtaagaca ccaaccttta cattcttccc 2220
tgaggttgtg gctgacagag cctgcttggc cccactgtta gtccagttag ctccatatac 2280
aaaatgccgt agcgcggtg gcttacaac aacagaaacg tattgtcac agtcttgggg 2340
ggctgggacg tccaagatca agagggcagc agattcggac tccgtgagg gctgttcccc 2400
gatccataga tgggtgcctt tcgctgtatc ctcaatggta gaagcacaaa caagcaagct 2460
ccttctgccc tcttttataa ggactccaac cctgttcatg agggctctgc ccccatgacc 2520
caatcagctc caaaggcccc acctcctaata actgtcacct tgggggtgag aattccaatg 2580
tgaatttgca ggggagtg gggacacaca caaatttcgg ggccatacca ccttcacca 2640
caccctctg cgctcagggg ggcttgcagt ccttggccct tctgttgggc atttggtag 2700
tcttttctct tgggtgatt tctgatgtt ttactctata tagtgaaaag ctaggagag 2760
cgggtcttct cccctctccc tctccagtc cctcacatc ccagatgggt tctaatagcag 2820
ctgctggggc ctgatgccct gagttgtttg tgattcaata aagaatccat aagaaaaaaa 2880
aaaaaaaa
```

<210> 36

<211> 2323

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2057214CB1

<400> 36

```
ccctcagcgg cgcttctctg tagcgagcct agtggcgggg gtttgcattg aaacgtgagc 60
gcgacccgac cttaaagagt ggggagcaaa gggaggacag agccctttaa aacgaggcgg 120
gtgggtgctg cccctttaag ggcggggcgt cgggacgact gtatctgagc cccagactgc 180
cccagatttc tgcgcaggc tgcgaggaag gccccttagg ctgggtctgg gtgcttggcg 240
gcggcggtt cctcccgcgt cgctctcccc gggcccagag gcaccteggc ttcagtcatg 300
ctgagcagag tatggaagca cctgactacg aagtgcctatc cgtgcgagaa cagctattcc 360
acgagaggat ccgcgagtg attatatcaa cacttctgtt tgcaacactg tacatcctct 420
gccacatctt cctgacccgc ttcaagaagc ctgctgagtt caccacagtg gatgatgaag 480
atgccaccgt caacaagatt gcgctcgagc tgtgcacctt taccctggca attgccctgg 540
gtgctgtctt gctcctgccc ttctccatca tcagcaatga ggtgctgctc tccctgcctc 600
ggaactacta catccagtgg ctcaacggct cctcatcca tggcctctgg aaccttgttt 660
ttctcttctc caacctgtcc ctcatcttcc tcatgccctt tgcataattc ttcactgagt 720
ctgagggctt tgctggctcc agaaaggggt tcttgggccc ggtctatgag acagtgggtg 780
tggtgatgct cctcactctg ctgggtgctg gtatgggtgt ggtggcatca gccattgtgt 840
acaagaacaa ggccaacaga gactcactct atgacttttg ggagtactat ctcccctacc 900
tctaactcat catctcttcc cttgggggtt tgctgtctct ggtgtgtact ccaactgggtc 960
tcgcccgcgt gttctccgtc actgggaagc tgctagtcaa gcccgcgtg ctggaagacc 1020
tggaggagca gctglactgc tcagcctttg aggaggcagc cctgacccgc aggatctgta 1080
atcctacttc ctgctggctg ccttttagaca tggagctgct acacagacag gtccctggctc 1140
tgcagacaca gaggggtcct ctggagaaga ggcggaaggc ttcagcctgg caacggaacc 1200
tgggtacccc cctggctatg ctgtgcttgc tgggtgctgac gggcctgtct gtgctcattg 1260
tggccatcca catcctggag ctgctcatcg atgaggctgc catgccccga ggcattgcagg 1320
gtacctcctt agggcagggtc tcccttctcca agctgggctc ctttgggtgcc gtcattcagg 1380
ttgtactcat cttttacctt atggtgtctc cagttgtggg cttctatage tctccactct 1440
tccggagcct cggggcccaga tggcacgaca ctgccatgac gcagataatt gggaactgtg 1500
tctgtctcct ggtcctaagc tcagcacttc ctgtcttctc tcgaaccttg gggctcactc 1560
gctttgacct gctgggtgac tttggacgct tcaactggct gggcaatttc tacattgtgt 1620
tcctctacaa cgcagccttt gcaggectca ccacactctg tctggtgaag accttactg 1680
cagctgtgct ggcagagctg atccgggctt ttgggctgga cagactgccg ctgcccgtct 1740
ccggtttccc ccaggcatct aggaagacct agcaccagtg acctccagct gggggtggga 1800
aggaaaaaac tggacactgc catctgctgc ctaggcctgg aggggaagccc aaggctactt 1860
ggacctcagg acctggaatc tgagaggggt ggtggcagag gggagcagag ccattctgcac 1920
tattgcataa tctgagccag agtttgggac caggacctcc tgcttttcca tactraactg 1980
tggcctcagc atggggtagg gctgggtgac tgggtctagc ccctgatccc aaatctgttt 2040
```


WO 00/56891

PCT/US00/07817

PF-0681 PCT

```

agttttgcaaa cacagtggcg gagaaggtgg accggtctgcg ctcttggcag aaggtctgtct 360
tctactgcgg gatggcggtc gttcccatcg tcatcagcct gacctgacc acgtctgtgg 420
gcaacgccat cgcttttgc acgggggtgc tgtacggact ctctgtctg ggcaaaaagg 480
gcgatgcgat ctctatgcc aggatccagc agcagaggca gcaggcggat gaggagaagc 540
tcgcgagac cctggagggg gagctgtgaa gggctgggcg cccctccctc cctgtccctc 600
ttctggtctt gtgtgggtcc aagtgaggcc tggactgtcc acgtgaggc acagcctgga 660
gaggggcctt tgcacgtgtc cctacacctg gagtcctctg ctctttctc cagactggt 720
taagccagga gccactggct gctggtgtga gggctctggc tgtggactt gaggcagagc 780
ctgcagcagc tgtgtggaca ctaccagcc ctactcctct gctgggtggg tctgcagatc 840
tcacaccaca gacagggctg cctgtgacct gctgtgacct gggagcagct tccctggag 900
atgctgggtc tggcttgagg ggaggggcaa gtgggacctg gccacctggg cactgagcag 960
agggacctcc ccagctctc ttagcaggtg gagccccagg gctgggaca gctgcccgt 1020
gccagcaacc tccactgct gcctagggtg cagcgccac tgtaacctg ccttctgaag 1080
aagcccacag ggctcctaag gtgcaccccg gtacctgga ctgcagcctt ggcagtgaact 1140
ggacagctgg gtgggggatg ctccctgctg gccctgggaa ccttggacag gccacctcaa 1200
ggccctcgg ctgcccctcc tccctgggccc tgtggggccc cctaggttct gccatcacc 1260
cccgcacct gctggccttg gtgctaagg agtggggaga gcaggctctc cctggcaccg 1320
aggggtgcca cctctccct ggtgtggccc cgtcaacatc agccacagcc cagccctatt 1380
agtgggttag tgggtctgac ctacagccca ctacaggtct cctgctggcc tgcccaagcc 1440
ctgcccctcag ggagcttctg ccttttaaga actgggcaga ggcacagtc acctcccac 1500
acagagctgt cccactgcc ctgggtgcca ggtctgccc agccaggcct acccaggag 1560
gatgcagaga gctggtgccc aggatgtgca ccccatatt cctctgccc tgtggcctca 1620
gcccgtggc ctctctgacc gtgaggctgg ctctcagcca tcgggcaggt gccgtgctg 1680
gctggttga gccaggtgg ggcttggcag aagcggggcg gtgtggaaga tattccatct 1740
ggggccaacc ccaggctgg cctgcgctga gcttctggag cgcaggtaact gggctctgct 1800
aagtgaactg tttcccagga acacctctcg ggcccatctg cgtctgagge tgggagtggc 1860
atctgagggc gggagtggca tctgaggcca ggaagtggcag gctgggtggc tgggcgtggg 1920
gttttctggg cctgcccag tactgccctg gggacttggg gggctcctg gtcagcagca 1980
tcccacctct gggagtctgg ccagctgagc cccagggtgg caggggcatt atagcctgg 2040
ggacatgtgc ctacaggtt cctccggggc caacttctc aggcagtg cgggttcaaa 2100
gggctgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtatgta tatgtgtgtg ggtgcacaca 2160
tctgtcccat gtatgcagtg agacctgtct acctcccaca aggagcaagg gctctgccc 2220
ccctctgtc attcctaccc aggtagtggg accccggggc ccttctgccc tggcttgcct 2282
gc

```

<210> 39

<211> 967

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3487228CB1

<400> 39

```

ggacagctgg cgccggcagc agcggaccgg cgggagacgg cggcttgcga gctggctgtg 60
ctgcaggagc tgcggcagcc gccgtccttg cacctaagga acctctgctg ccagcccttc 120
ctcacttttg gaaatggcgg gtgaaattac agagaccggg gaactctact ctccctacgt 180
tgggctgggtg tacatgttta acctcatcgt gggcacgggc gactcacca tgcccaaggc 240
attcgccact gccgggtggc ttgtcagcct cgtcctgctg gtgttctctg gcttcatgag 300
cttcatgacc accacctttg tgatagaggg catggctgca gccaacgcgc agctccactg 360
gaagaggatg gagaacctca aggaggagga agatgacgac tctccacag cctcagacag 420
cgatgttctc atccgggaca actacgagcg ggcagagaag cggcccatcc tgtctgtgag 480
taagtcttgg ggttctcgcg ggcccgcact tccctccggg ccacagggtt cctttctctc 540
atggagaggg ccttgagag gctcccgcga gattctggca tttcctgccc ctgggttctg 600
aggcaggccc tgtggttagac tcaaaagage acagggttcc agtccctggg acagtccctg 660
cccctgctgg cttggccact actcagattt gcagcttggg aagtctcctg acctgtgcac 720
ctcagtttcc ccccatacc ctctctgcta ctgagatgat taaatgcctg gttcctgccc 780
tgggtcaccc tggaaagctca agtagatglt gttctgtggc atctcttctt cctcctgccc 840
tgtgccctca tgttcataca tggccctgcc ttgctgtctc ctccctgggc ggctgggtta 900
ggctctgacg cctgctctcc ctttcacccc agcaggagca tctctgaatt cccttaaaaa 960

```


WO 00/56891

PCT/US00/07817

PF-0681 PCT

```

ctcactagtc ggcggccgct tgggcgcact tgccgggtca ccttgtcccg gaggagaaat 60
ggcttccctg aggcaagtgt aacctacatt cccagccac cagcctgacg cccagccagg 120
gagagagtac catggatggc atcattgaac agaagagcat gctggtgcac agtaaaatca 180
gtgatgctgg caagaggaat ggtttaatta acaccagaaa cttgatggcc gagagcagag 240
atggtctggt gtctgtttac ccagcgcccc agtaccagag ccaccgggtg ggggccagca 300
cagtgcgggc cagcctggac agcagcagga gtgagccgat gcagcagctg ctggaccca 360
acacctgca gcagtcagtg gagtcccgct accggcccaa catcatcctc tattcagagg 420
gcgtgctgcg ctctggggg gacggtgtgg ccgcccactg ctgcgagacc accttcacg 480
aggaccggtc gccaccacaa gacagcctcg agtaccggga tgggaagttc attgacctct 540
cagctgatga cataaaaatc cacacctgt cctacgatgt ggaggaggag gaggagtcc 600
aggagctgga gagcgactac tcaagcgaca cagagagtga ggacaatttc ctcatgatgc 660
ccccgcgga ccacctggg ctcagtgtct tctccatgct ctgctgcttc tggcctctgg 720
gcategcagc cttctacttg tcccatgaga ccaacaaagc cgtggccaag ggggacttgc 780
accaggccag caccagctcc cggcgggccc tattcctggc agtgctgtcc atcaccattg 840
ggactggcgt ctatgtgggc gtggcgtggc cgtggccctc atcgccacc tctccaagaa 900
caaccacctg tgagcttctt gcgaatggag ggggagcacc cggggccagg tctgtgtgga 960
cgtggaggaa gcaggcatac cgcatgatgc tgtacagtac aaatgattgc caaatgatgc 1020
cacgaagccc tgggatttcc taccatgga tttattttgt ttttatectt taatttcatg 1080
ttcacagcac tgtgtagagc accagacaga cgggcactgc taatccttcc aaaggaaagc 1140
tccaaagatc ccagcccgca aggctgtctc tggatggalt ctggtggatg aatggcaacg 1200
cggctctctg cagcctgcca gtgccagag tgccaccgca ttagcaatat acaaacagtc 1260
caaaaaagtg tttatttttt atggaatacg gtgcaatagg cagaggacaa gggacacatc 1320
actcttctgt ctgtggccct gctggagtc tttgtgcccc ccggagtcca cagccttcc 1380
ctgcaagacg agaatggggc tgggaagaaa gaggcaacac cacggctggc aggagccccg 1440
ctgcaactgt ctgcagacc cttggcctga ccttgagaag cagagccagc aaagcccggg 1500
acctgcccc ctttctttcc cttcacacca cccagcctc aggatgtcaa gccacctccg 1560
gaacgtgtct acactccaca gctacccgc agcaatacgc actcttggga cctcgctgat 1620
ctaggatggg gaggcaggcc accgcccctc ccaagactcc tcaagaaaga gccccgggt 1680
tgctccggaa actcgaggca ctgcagctat gggcactgcc tcagcctaaa gacacagggg 1740
cgctcccaa tcaccgcgt ggcggtgct caccctgtca taagcagaaa ctagtgatcc 1800
tggaaatgag atgggcctta ctctgtcgag taaatgaata gctattttct tgtcattttt 1860
taaagtgcaa ctcttgcttc atgctgctta agttaccaga tgaatgctga gaaataagta 1920
atcacagaca ttttaatacc atttcattgc tgttttacga gtgttcatta cttaacaaaa 1980
aattatcttt taaaaaaaaa a 2001

```

<210> 42

<211> 1170

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 4069777CB1

<400> 42

```

gctcagcacc ggggtctgtg tccgagtggg gatggctctg ggggctgagg atactgtgca 60
ggccaagcgc tcggccgtct cgggcgtgct cagcatagtt ggcatttccc tggctctggg 120
cagcctgata agcatccttg aacatcagct ggggcataatt tttaccaatg atgagtagag 180
atgtcattgc cctggtgagc caggtcttgc cggtttatag tgtttttcac gtgtttgagg 240
ccatctgttg tgtctatggc ggagtctctga gaggaactgg gaagcaggcc tttggtgccg 300
ctgtgaatgc catcacatat tacatcatcg gcctaccact gggcatcctt ctgaccttgg 360
tggtcagaat gagaatcatg ggctcttggc tgggcatgct ggcctgtgtc ttcttggcaa 420
ctgctgcctt tgttgcctat actgcccggc tggactggaa gcttgcctga gaggaggcta 480
agaaacattc aggcggcag cagcagcaga gagcagagag cactgcaacc agacctgggc 540
ctgagaaagc agtcctatct tcagtggcta caggcagttc ccttggcatt accttgacaa 600
cgtattcaag gtctgagtgc cacgtggact tcttcaggac tccagaggag gccacgccc 660
tttcagctcc taccagcaga ctatcagtga aacagctggt catecgccgt gggctgtctc 720
tggggcgccc gtcagccaca ctgatgggtg ggtcacgggt caggatccta gccaccagcc 780
actagcaaa gagcttggaa atagaaagcc aggagtggct gtccccagta tgcaaacaca 840
ccacggctct cctgcaaaa acaccaatgg ggtctagtgc aggtggacac tttgaaccac 900
tctcaaaaa aaagaacttt ggctgattcc ttgtggtgac actcagaggg gtctgaacag 960

```


WO 00/56891

PCT/US00/07817

PF-0681 PCT

```

ttagttcaca gtttatggcg tatattgaac agcggcgaat ctctcatgag ggttcaccag 240
taaagccagt agccattagg gagtttcaaa aaacagaaga tatgagaaga tatttacatc 300
aaaacagggt tccagctgag ccattctccc tctgtcact atcagcaagt cacaatcagc 360
tgtcacacac agacctggaa cttcatcaga gaaggagca gttagtagag cgcactcgga 420
gagaggctca gcttgctgcc ctgcagtatg aggaggagaa aataaggacc aagcagatcc 480
agagagatgc tgtcctggac tttgtcaaac aaaaagcatc acaaagtcca caaaaacagc 540
acccgctect agatggcgta gatggtgagt gccccttccc atccagaagg tctcagcaca 600
ctgatgatag tgccttgtgc atgagtgatg acagacctaa tgctctatta agttcacctg 660
caacagaaac agttcatcat tcccctgcat attcttttcc tgctgctatc cagagaaatc 720
agcctcagcg ccttgaaagc ttccctttcc gagcagggtg cagggcagaa accaacaag 780
gtcatgcttc accccttccc ccattctgctg cacctaccac tgattctaca gattccataa 840
caggacagaa ttcaagacag agagaagaag agctggaatt aatagaccaa ctgcgtaaac 900
atattgagta ccggttgaaa gtgtctctac cttgtgatct cggagcagct ctaactgacg 960
gtgttgttct ttgccatttg gccaatcatg tgcgacctcg atctgtccca agcattcatg 1020
ttccctcacc agctgtacct aaattaacaa tggcgaaatg caggcgaaat gtggaaaatt 1080
tctagaagc ttgcagaaaa attggtgtac ctcaggacaa tctttgttcc ccttccgaca 1140
tccctcagct aaacctcagc gttaaaagaa ctgttgaaac gctcctttct cttggggcac 1200
actcagaaga atccagtttt gtctgtctct ctctgcagct tctgggtttt gtggcatttt 1260
actgtactgt gatgttaact ctctgtgtgc tttattactg gctcttcccc gctcgtgaa 1320
agattgcact ccggtgaact tctgctcat tctgtgctt ggtaaaggag gagcaattat 1380
gtttgacctt ccacatttta gaagagaaag gtttgagcca gggtgcagtg acggtccagg 1440
ctctcctgga acttgcccca cccaagcaac agcagcacca gttatctgct gtttgaggat 1500
ccccaggacg gtgggcaact gcctggccaa aacaaggaaac aggacaccgt gattgctgct 1560
gccagctatc tgcttaaaaca aagctcttgt gtgttctcag aagggaaccgt tcccatgatt 1620
cctaacagga atattttgct tcatttctcc attttagggg aggttatttc cattccatt 1680
gaattttttt acgaagacac cattggtttt ctcagatgaa acttctctta ctgaaaaccc 1740
agcacctaac ttggtgtgt tttcctggag agcaggcgtg tttcacgtgc cagaaagcac 1800
atcttctgtg ttaggcacaa gcatgctgtg ccattgtttt tacctggctc caagacaact 1860
ggctctgctg tttctaaact tgggtgttca ttagactctc ctggagtatt tgtaaaaata 1920
cagattcaca ttcagtagag ctggggtaag gcttaggaat ctgcattttc aacaaccact 1980
gcactccagc actggcaaca gacaggatcg gagggcgcca ac

```

<210> 45

<211> 1877

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 483751CB1

<400> 45

```

tgacggccgc ctcccggtta cccgggactt ctggagtcgg agaagtcaac ggcgcggttg 60
ctgcccgcgc cgcgctcccc ggcccagggc gatggagaac ggagcgggtg acagcccac 120
tacggaggag gacccgggccc ccgccagagg ccccccggagc ggctcgtctg cctacttttt 180
catgggcccgc ctcccattgc tccggcgcgt tctcaagggc ttgcagctgt tgctgtctct 240
gctggccttc atctgtgaag aagttgtatc acaatgtact ttatgtggag gactttattt 300
ttttgagttt gtaagctgca gtgcctttct tctgagtctc cttatactga ttgtgtattg 360
cactccattt tatgagagag ttgataccac aaaagtaaaa tcatcggatt tttatattac 420
tttggaaca ggatgtgtgt ttttgttggc atccatcatt tttgtttcca cacatgacag 480
gacttcagct gagattgctg caattgtgtt tggatttata gcaagtttta tgttcctact 540
tgactttatc actatgctgt atgaaaaacg acaggagtcc cagctgagaa aacctgaaaa 600
taccactagg gctgaagccc tcactgagcc acttaatgcc taaagactct ggggagcaga 660
tgttacctaa ggtagtgaac ctgcattgtg gtgcctgagc cctggcagaa gctcttgtaa 720
aatttgttaa ttgtttaaac cacttctttt ggagagcaag ggggaaggta agaaggcagt 780
tttatcaata ttgtgtcagt caccacaaag taggccagat aagttaaaaa aaattttttt 840
ttaaataata attgaaactt atctcaaatg gagatttttg tgggaggagg agaaaacaat 900
tgtttttaaa tcacacagct caacggttga taaatgattc gctttatagc tgtataaaca tctgtgattat 1020
ttcttttact aggcctagct tccaaattat gctttatagc tgtataaaca tctgtgattat 1080
attcatctac ttagaaattg ttttattttt aaattaattt gcttagctgt ttgttttgat 1140
gcttagatta tgttctgtta atgggaattt aacataattt agaaaccaat atttaaaatg

```

WO 00/56891

PCT/US00/07817

PF-0681 PCT

ttggtctagg	tttttttctt	taacatatat	taccaggctt	tactgtat	cactcagcct	1200
taaatgttat	aataattttt	gataacggtt	attaattctt	tgagacctt	gtatagccta	1260
taaaatgtat	gggagatggt	ggtattttat	gtgtataaaa	gcaacaatat	cagcaacttc	1320
gtgtttatac	tgcaccttgg	ttgttgatgt	caagtaaaaa	aaagattggt	ttgtaacaca	1380
taaaaaaatg	gaagaaactg	ataccacacc	taaggaccaa	agataagaaa	gactttttgc	1440
ccaagacagt	gaaaagtaatt	ataaaaacaa	gctttgacca	cttaccaagt	atctgaagag	1500
atgagttcat	actatgattt	agaaagtggg	tcaattcccc	tggtggcata	tgattatttt	1560
tactaaaatt	aatacagctc	tggtgggtctt	ccttagtggt	ttctttgaag	ccaatctggt	1620
tttttttagga	caccagcctt	tggtttttca	tctgttcgag	atgctctctc	tctgtctcct	1680
tatcagatag	aaatggagtc	atgtgctgct	gcttcatcta	gcagagggtg	gcctctggct	1740
ctgacacttt	ttgtcagttg	tcttttaggtg	gtcctgaatc	ttgggccctt	ttgattgtga	1800
atactgtgta	gcaggatctt	gagagtcctt	gttcttacat	aggcattgct	ctagtttgct	1860
tttggcaaaa	aaaaaaa					1877

<210> 46

<211> 2382

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 727332CB1

<400> 46

tatcagcagt	aagtgccttc	atatttttgt	tcatcaaaag	tgaaatacca	aataacacgt	60
gttccatgga	taccactcca	ttaataacag	agcatgtgat	caacacaacc	caagaccctt	120
gttccctgggt	ggataaactt	tctacagtac	accaccgcat	agtgggctgc	agtcttgcag	180
tgatatctgg	agtactctat	ggatctacat	ttgtgccaat	catctacatc	aaggaccaca	240
gcaaaaagaaa	tgatagtata	tatgcagggg	caagccaata	tgatttagac	tatgtgtttg	300
cgcacttcag	tggcatcttt	cttacaagta	ctgtctactt	tctggcctac	tgcatagcca	360
tgaaaaatag	tcctaaacta	tatcctgaag	cagtcctacc	aggattcctg	tcaggagtac	420
tttgggctat	agctacctgc	tggttggtta	tagcaaatca	ctctctgagt	gctgtgggtca	480
gtttttccaat	aatcactgct	gggtccaggat	ttatagctgc	aatgtggggg	atcttcatgt	540
ttaagggaat	aaaggttcta	caaaactacc	tattaatgat	acttgcat	tgcatcatct	600
tgactggagc	cttatgcact	gctttttcta	aaatctaaca	atgacaaaac	cagcaggtgg	660
cagcagtagt	taagagaacg	cgtctatcgg	acagcggaga	gatcatgctg	agaaaagagt	720
gcattttcat	atagcaaatg	gatctcagcc	actgttggag	tgggtaaaatg	attttttccc	780
ccaaaaatgt	gagaatgaag	gaagattgag	tttcattcaa	gtataaaaaat	gaaaatttct	840
tctgatgaac	tgtttatgaa	ggtagtactt	tactgggtga	ctaaaatgtc	tacattatta	900
tagcattaca	tacgaggatg	ctctttttac	cacagtatgt	acctagtgtt	gcataatcta	960
gaacacagta	tagagtccat	atacaaagaa	gttacagctc	atattttctca	cctattacc	1020
cagtgaagtg	aggcagaaat	accttgggag	aggagggaga	gccttacctt	ctaattggaat	1080
tagattccaa	agatatttgg	atccttttgt	tcataaagta	aatgcatagt	tggttaactaa	1140
atgttaaaaa	ggccatttta	ttattgttag	ccaaaacttc	tgtttatttc	aagttaatat	1200
cgccecaactc	tacatcatct	acctatttta	gttcataatg	cttttgatta	tcgccagata	1260
aagtccattc	tcagagaaca	aaaatttttc	atcattgaga	aaatgtgcat	aacataatac	1320
atacatcac	aagtatatte	acgtacataa	atacacacag	atatgttgct	aaagtggagt	1380
tgtaggttat	cagtaacaat	ttaaaggaaa	caaccactct	tttgaatgta	caactttttt	1440
ttctgaaata	cactttttcta	aaacctctct	aactggaggt	ttcctgtttt	cttcttgttt	1500
taactgggtgg	tttccagtag	gcaaaataaa	atgacaggca	tgctagtttt	tttttttttt	1560
tttttttttt	aagaaaactg	aaattaagcc	aggcaggggtg	gcgcactact	ataatcccag	1620
ctgctggggg	ggctgaagta	ggaggggtcac	ttagcccaag	agtgcacatc	tgccagccta	1680
ggcaacatag	caaggtccca	tctctaaaaa	agaaatttaa	tttaaaattg	taagaaaaaa	1740
gaaaactgaa	acagaactgc	cagtlacaatg	tttgttgcaa	ttgtttccaa	aactttgaaa	1800
taacgaaacc	cctattcaaa	tgtaaatttt	acctattccc	acctgatagt	actgtttatt	1860
actttgctat	gcaggagaaa	caaaacagct	ttttatttgt	gtgtatactc	tgaagtcaat	1920
gtgcatgggt	taaatcccac	ctctgcttca	ttttatttgt	gtggcttttg	acaagttcct	1980
aagccctctg	tgctaggccc	ctcattaaca	aaatggagtt	tatgatggca	tctacctcac	2040
atggttattg	tgtggttgaa	attagttcaa	atctgtaaag	tatgttgatg	agtatctggt	2100
acttggcaaa	cactatataa	ttgttagctt	tattattatg	tggtgtttga	agggaaaaaa	2160
agtttttgta	gattggagaa	caccatgtaa	gagctactaa	gtccaccacc	ttcccatcca	2220

WO 00/56891

PCT/US00/07817

PF-0681 PCT

aacaattatt	actcctctaa	atgaatacta	cttaaaagtg	atggagcttc	tgtttgttta	2280
ttgaattgct	aatacaaata	aatatttgac	tataacttct	tatactcatt	ttaattttta	2340
cctgaaatgt	cattaaatta	tgctgataaa	ctttgaataa	at		2382

<210> 47

<211> 2383

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 778800CB1

<400> 47

cttacaatca	tctctgcttct	tgtacatcac	tgaattttca	tctcattgat	tatcatctgg	60
cagcattcat	cacagtgatg	cttgcgagga	ggcttgatg	ggctctcatc	tcagaggcta	120
ctaaggcagg	tgcagcatca	atgattcact	acatggttct	gatatcagct	cgcttggtac	180
tactcacttt	gtgtggatgg	gtactttggt	ggaccctcgt	caatctcttt	cgaagccatt	240
cagtcctcaa	tctccttttc	cttggtctacc	cgtttggtgt	ttatgttcct	ctttgctggt	300
ttcatcaaga	tagtagagca	catcttcttc	tcacagacta	caactatgtg	gttcagcacg	360
aggcagtaga	ggaaaagtgc	tcgactgtgg	gaggcttggc	caaatccaaa	gactttctct	420
ccttggtgct	ggagtcgcta	aaagaacagt	ttaataatgc	cacacccatc	cccaccaca	480
gttgtccctt	atctccagac	ctcattcgca	atgaagtaga	atgtctgaaa	gcagatttca	540
accacagaat	caaggagggt	ctcttcaact	cctctctcag	tgcctactat	gttgcatctc	600
tccccctgtg	ttttgtgaag	agtacccagt	actatgacat	gcgctgggtc	tgtagcgacc	660
tcattatggg	gtggatcaat	gcttttgtca	tgctcaccac	gcaactgttg	ccatccaaat	720
actgtgattt	gtacataaaa	tcagctgctc	acctgggcaa	gtggcagaag	ttggaacatg	780
ggctctacag	caatgctcca	cagcacattt	ggtcagaaaa	tacaatatgg	cctcaagggg	840
tgctggtgcg	gcacagcaga	tgtttatata	gagccatggg	gccttacaac	gtggcaggtc	900
cttcagatgt	atctcatgcc	cgcttttatt	tcttatttca	tcgaccatta	aggctgttaa	960
atctgtcat	ccttattgag	ggcagtgtcg	tcttctatca	gctctattcc	ttgctgcggt	1020
cggagaagtg	gaaccacaca	ctttccatgg	ctctcatcct	cttctgcaac	tactatgttt	1080
tatttaaaact	tctccggggac	agaatagtat	taggcagggc	atactcctac	ccactcaaca	1140
gttatgaact	caagacaaac	taagctgcct	ctcaacaatg	agggagaact	cagataaaaa	1200
tattttcata	cgttctatit	ttttcttgtg	atttttataa	atatttaaga	tattttatat	1260
tttgtatact	attatgtttt	gaaaagtcggg	aagagtaagg	gatattaaat	gtatccgtaa	1320
acaaggtagt	gtgatctttc	atgtgttagt	atattcgaat	aataacata	tgagaggtat	1380
gcctgtccag	taaagagatt	gatttgtttg	tatggctctg	gaataactca	ttcgtttatg	1440
aacacatctc	atgtattact	tgacacagta	cctttgggtat	gtctgctttt	ctttcaatcc	1500
tcattatctt	tagccctcag	ctggccagta	cttattgcta	aagaaaaggga	gatcaatgga	1560
gttgccctacc	agcaccctatt	ctcttttagt	tcagctggct	aatagtattg	gaatacattg	1620
ggaaaagagt	gggttaaagt	cctaggtggg	gttctctttg	ttgcctacca	ggagaaaagca	1680
gtaggettcc	tttctaagat	acggactcag	ctggctctatt	ttaccctgtg	acattttaa	1740
atacttttga	ataagctact	atcctgagge	tgagggtttt	gctgccactt	ttcctgtgtt	1800
tccactttctg	cttccaaaga	ttttcctctt	agttgtttga	aataataactt	tgccagacag	1860
gaagtcttta	gactgcccac	attcatgaag	aagatgatgt	gtggctggat	cagtaggaga	1920
agctgagtgc	aaatgccatg	tgggctagag	tatgggaagg	ttgaaaattc	caagtaactg	1980
ggagagtggg	caagtcctca	gctgaacaat	cttggtatgta	gtctagcagc	aaccaccta	2040
caatggcggt	atgtttggag	ttatgagggg	aagtgaagaa	taagaattac	ctacagcttt	2100
gtactcagat	aatttatatc	caaaattttgt	gttttaaat	tcatactcca	gaactttcat	2160
gtttatgagt	attagccttt	taagttatgg	gaggtgatat	acttagtcca	ttgatgttgt	2220
cacttgtcat	ctaaacttat	gagaccttgt	cttagagaat	ctaaaatata	ttgtcatatg	2280
ttttctgtgc	tgagtttggg	ttgttacact	gtgaagcttt	tggtgaaaca	aaataagact	2340
tatgaagtaa	aaagaccaat	cgtgtcgttg	aaaaaaaaaa	aaa		2383

<210> 48

<211> 1344

<212> DNA

<213> Homo sapiens

<220>

WO 00/56891

PCT/US00/07817

PF-0681 PCT

<221> misc_feature

<223> Incyte ID No: 1396995CB1

<400> 48

```
cacgcgtccg cccacgcgtc cggcagcatg tatgtgtcca gtcttcatta tcaactatat 60
gacccaaaga aagtaccaca tagtggtagt aaatattgat ttcagccacc aacagactca 120
tgtattcttc tagatgtcaa aggaaaattt tgtgaggacc actgtatat acagcactct 180
aaccggtaag caaattggga attttaaatt atcaaaaatt ttttttttcc tggattgta 240
gcctggtagt gtcttgggtt cttggattga acaaatgttc actaaacaaa catgcattaa 300
ttatcttcta ctgtgttgaa atgggtattat tataggagtt tgtttggcaa gaatgagtat 360
tccagtgcct ggccactctg aacacataaa tttgattact gcaacatcca aatggaggac 420
cacatcatca gctgctactt gaagtggcca gtctgtgccc aactactgaa ctgttcagag 480
cccacagaaa gggctacggg agagacatgt atgggtatctc gtatacacag gcatgcctta 540
tttctttgtc ttctacccca gtgctaccta cctaaagacc tctggctactc ttccctttcc 600
tgggaaagaa attcaatctt gttttctctt ttattattgt attctctatt ctacagttaa 660
gccccaatag tagccaaagg aaaaaggggg aagatgatag tttgactaaa caaataccag 720
ttcatacatt cttgttccaa taggagttat gggaggaaaa attattccaa gcaatcacac 780
aggatcaact tttctcctt gtagaatatg tgctatcaca ttggcagaat ctcatccagt 840
tcttcaaagt ggaaaaacaa ttaaaagcat ttcctatcag atcagtacca actgtagcac 900
acttcagaac aagggtctctg ggaaatttaa gcgggtatgt tcctgtaatt ctgtgattat 960
ctacttacat cctctatatt catggtaatg acagatccaa tgaactttag aatccagtag 1020
catatgctta gcatacttct cttagcagttt gaggtgctaa ttttaggtat actttcacct 1080
aaagaaattc tcagctcccc caaatttaggt atctcaggag gtgtagtatc tgttatatta 1140
ggttctgtgc tactatccct ataattgccc ggatggagga gggggaaggc aggcctttga 1200
aaggagaact ctaatagcaa tataacaaga tattttgtcc cttctagtgt tattaacta 1260
gtatgtcgag ttctgtaaaa tttagggtgac taactcttct ttaccatata tttccacatg 1320
taaattaaac agaaaaaaaaa ttgc 1344
```

<210> 49

<211> 800

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1597730CB1

<400> 49

```
gcgctggaag ccctggcggc ggcggeccat ggggccccttg gcgctgcccc cctggctgca 60
gccaggtat aggaagaatg cgtatctttt catctattac ttaatccagt tctgtggcca 120
ctcttggata ttacaaaata tgacagtcag attcttttca tttggaaaag attcaatggg 180
tgacactttt tatgctattg gacttgtgat gcgactttgc caatccgtat ctctectgga 240
actgctgcac atatatgttg gcattgagtc aaaccatctt ctcccaaggc ttttgcagct 300
cacagaaaga ataatcatcc tttttgtggg gatcaccagt caagaggaag tccaagagaa 360
atatgtgggtg tgtgttttat tcgtcttttg gaatctattg gatatgggta ggtacactta 420
tagcatgtta tcagtcatag gaatatccta tgctgtcttg acatggctca gtcaaacact 480
atggatgcca atttatcctt tglgtgttct tgctgaagca tttgccatct atcaatcgct 540
gccttatttt gaatcatttg gcacttattc caccaagctg ccctttgact tatccatcta 600
tttcccatat gtgctgaaaa tatatctcat gatgctcttt atagggtatgt attttaccta 660
cagtcaccta tactcagaaa gaagagacat cctcggaatc tttcccatia aaaaaagaa 720
gatgtgaagt acagcattcc agtgtgacac gagaaaagac aggcgtgtgga ttcagtgcag 780
taaataaaac acgaggaagg
```

<210> 50

<211> 1505

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1629304CB1

WO 00/56891

PCT/US00/07817

PF-0681 PCT

```
<400> 50
ggcgggcgggg cgctccggggg aggccaggac agctgatggt tgtggcagaa acatctcaag 60
gtagctgggtc cgccccact tccccatcta cctcttgtec tcccccaac accaccacca 120
ccctggctec cctccctcat gaccgcctgg atcctcctgc ctgtcagcct gtcagcggtc 180
tccatcactg gcataatggac tgtgtatgcc atggctgtga tgaaccacca tgtatgccct 240
gtggagaact ggctctacaa cgagtcctgc cctcctgacc ctgctgagca aggggggtccc 300
aagacctgct gcaccttgga cgatgtcccc ctcatcagca agtgtggctc ctatccccc 360
gaaagctgcc tcttcagcct cattggcaac atgggtgctt tcatggtggc cctgatctgc 420
ctcctgcgct acgggcagct cctggagcag agtcggcact ctggggttaa caccacggca 480
ctcatcacag gctgcaccaa cgctgcgggc ctcttggtgg ttggcaactt tcaggtggat 540
catgccaggt ctctgcacta cgctggagct ggctggcct tccctgcggg gctgctcttt 600
gtttgcctgc actgtgctct cctctaccaa ggggccaccg ccccgctgga cctggctgtg 660
gcctatctgc gaagtgtgct ggctgtcatc gcctttatca cctggtcct cagtggagtc 720
ttctttgtcc atgagagtct tcagctgcaa catggggcag cctgtgtga gtgggtgtgt 780
gtcatcgata tccctatttt ctatggcacc ttcagctacg agtttggggc agtctctca 840
gacacactgg tggctgcact gcagcctacc cctggccggg cctgcaagtc ctccgggagc 900
agcagcact ccaccacact caactgtgcc cccgagagca tcgctatgat ctaaggctctg 960
gggaggggtgg ctggcccgcc ctccacagca cccaccccca tatcttcttt ccatttattt 1020
cgtacacaaa acaattttga gaaagtattc tgttgggatc tgggcttctt cacttctgga 1080
gaagtggcca tcccatgccc acctgtgcca tggaggagtg ggccctgcca gctgccacag 1140
ctgcatgacc tgcttcccca cccacgggtg tcgttttgtt tttaaaggtc acctgtcttc 1200
actacccag ccagcccttc aggtgccttc tactcccagt gccaaagcca gaccactggg 1260
gtttcctgct gcaggaattg ggggctggga acagcagagg ggatagaagt ctggtggagg 1320
tggagtgggc acgccttagc ctacggaaaag gccatttctt gggccactg agctgcactg 1380
ggattcttca cctgcccc cacttctttt agggcaataa acacagcaga accacgtggg 1440
tattttagta ctttttttta tattaaaaga attctaattt gcaaaaaaaaa gaaaaaaaaa 1500
aaaaa 1505
```

<210> 51

<211> 2744

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1989585CB1

<400> 51

```
gcacagttag cggacgcctg ggcgggcgggg gcgggcggt gatggctccg gccgcgagcc 60
gagagggcta ctggggcccc acgacctcca cgctggactg gtgcgaggag aactactccg 120
tgacctggta catgcccgag ttctggaata cagttagtaa cctgatcatg attatactc 180
caatgttcgg tgcaattcag agtgtttagag acggctctgga aaaacggtag attgtctctt 240
athtagcact cacagtggta ggaatgggat cctgggtgctt ccacatgact ctgaaatatg 300
aaatgcagct attggatgaa ctcccaatga tatacagctg ttgcatattt gtgtactgca 360
tgtttgaaatg tttcaagatc aagaactcag taaactacca tctgcttttt accttagttc 420
tattcagttt aatagtaacc acagtttacc ttaaggtaaa agagccaata tccatcagg 480
tcatgtatgg aatggttggtc ttacatttag tacttcgac tatttatatt gttacatggg 540
tttatccatg gcttagagga ctgggttata catcattggg tatattttta ttgggatttt 600
tattttggaa tatagataac atattttgtg agtcaactgag gaactttcga aagaaggtag 660
cacctatcat aggtattacc acacaatttc atgcatggtg gcatatttta actggccttg 720
gttctctatc tcacatcctt tttagtttgt atacaagaac actttacctg agatataggc 780
caaaagtga gtttctcttt ggaatctggt cagtcatcct gtttgagcct ctgaggaagc 840
attgatgaat cattccacca agaaaacaaa caagcaccta ccatagacct gccagaataa 900
ataaggaaat ccttaaagat ctacaagttc aaatatgtca tgaccatcac agcagaggag 960
tgactttctg actaatgctg ccaccacac agagaataag gagtagggcc tgcgtgggtgt 1020
ttagctcatg gctttatctt atttgtcccc ctctctcttt cagctccag tttataaaga 1080
aacagagatg atgtgtgtgt atgcctcaaa tgcgaataa gttgggcttt tcttaacagg 1140
ttaacagttt gtgctgggta taagaaatta accttctttt ctttttgcca aggggtgcat 1200
gtgaattata cttttcttaa tatttgatta aataatgcag tcagctaaga gccacacaaa 1260
ccccatatcc agatagttag ctgtgagcca gcactcagct gtgtcagatt tgattaatat 1320
tgtattaatc tcatggatgg ttctcaaagg taaaaaaga gagagaaaga gagagagcta 1380
```

WO 00/56891

PCT/US00/07817

PF-0681 PCT

```

gctgtgggat tctgtgtagt tcttcactat ctgttccagg gctagtcgga ggatcataag 1440
caagctcaga cctgccccca gttcagtact tgaccacatc ccaggattta tgggtgtctgt 1500
ctatggccac agccaaccag aatgagtggg tcattcttata acctttctga agctccatga 1560
ggacatgtat agaatgctgc accttcagcc agctctgtctc tgatcttllgc agatctttta 1620
ggtgtcactg tttctacggc tagacaaata tgactgggtgg tctagactac ccatagttca 1680
tctcctcac ataacttatt tgaagtgtgc agggaatgtc attacactct gattttttaaa 1740
attatgcagt attttccagt tctcagagag gtcattgggtg tgcccaggga agtgtgttgc 1800
attaactaaa gctaaaatta tcagaatcct atttacataa agcatattaa aatatctgct 1860
ccttaatttt ctgaaggaaa tagatgtaag tttctgctac ttgaaacctc cagaaccgac 1920
aaaaattagg gtgctaaaaa aatgacagtg aaatctcctc glaaggcagc tagttctaat 1980
ttgcatttga atgtataaca aattgcatca cttttcacaa acttaacacc tgccctggagt 2040
aaaaatctga tttgacctct ctgctcatgt ttcattcatat ttgtagctct gcattcattta 2100
gcatttttat gacttttttt gctttatata aattattgta aaatccagat tgtttttacc 2160
acatgatgac gtgactcagg attaaatcct gagctacagt ttcaaaagga aaatcatttt 2220
tttcttatgc aaagatggta aaacactgtt gtcatttttt ccagttattca ataagtagcc 2280
tttgtacaaa tttaaaacca aaaactatct tgttgttttt cttcacctac tagccttagt 2340
ttttaaccaa gtatccaagg atgtcaactt gacatccttc ccttagcatg ccaacaagcc 2400
attagactga ttcttccacc tacttttatg aacctccagg aagaaaaaca cttgccaataa 2460
cattaagaga actttgatcc tgccttaaga ggggtataaaa ctaaacattt tgaaggcaca 2520
gccataaga ctatacttga tttggcccc aaggattctg acttctgggt acatttcacc 2580
tgcagttacc tgggctatcg ggcgtgatac attttttaat tcattttgtt ttccaccatt 2640
ataatttaat acttttcagt tagatatacc tctgcattaa gaggtttata cagtgttaagg 2700
ttaagggcta tcggacatgg ccatgccgtt aaacatggga agac 2744

```

<210> 52

<211> 1679

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2134729CB1

<400> 52

```

tgactttggg ggcaccatgg accaaagtgg gatggagatt cctgtgacct tcatcattaa 60
agcaccgaat cagaaatata gtgaccagac tattagctgc ttcttgaact ggaccgtggg 120
gaaactaaaa acgcatctat ctaacgttta ccctagcaaa ccattgacga aggatcagag 180
attgggtgtat tggggcagac tgettcccga tcatctgcag ctgaaagaca ttctcagaaa 240
acaagatgag tatcatatgg ttcatctagt atgtacttct cggactcttc ccagttcttc 300
aaaatccagc accaatagag aaagtcatga agcattggca tccagcagca attctagttc 360
agatcattca ggatcaacaa ctccatcatc tgggtcaagaa accttgtctt tagctgtggg 420
ttcttctca gaaggattga ggcagcgtac ccttccacaa gcacaaactg accaagcaca 480
gagtcaccag ttcccatatg taatgcaagg aaatgtagac aaccaatttc ctgggcaagc 540
tgctccacct ggattcccag tgtatcccgc gtttagccca ctgcagatgc tatgggtggc 600
acagatgtat gctcatcagt attatatgca gtatcaagct gcagtttcag ctcaggccac 660
atcaaagtgc aacccaaccc agcctactac ttcacagcct cttaaatttg ccatgtttcc 720
tggagaagaa ccccaccag ctccaaacct agtggcccaa gaaaatcgac ccatgaatga 780
gaatgttcaa atgaatgcac agggagggtcc agtactaaat gaagaagact tcaatcgaga 840
ctggctagac tggatgtaca cgttctcacg agctgcgatt ctcccttagca ttgtatactt 900
ctattcttct ttttagtcggg ttatcatggg aatggggagcc atgtacttgg tttatttaca 960
ccaagctgga tgggttctct tttaggcaaga aggaggtcat cagcaggctc ccaacaataa 1020
tgccgaagtt aacaatgatg ggcaaatgac aaacaacttg gaacttgaag aaatggagcg 1080
tcttatggat gatgggcttg aagatgagag tggagaagat ggaggtgaag atgccagtgc 1140
aattcaaagg cctggattaa tggcttcagc ttgggtcttcc atcaccacct tctttacttc 1200
actaatacca gaggggcctc cccaggttgc caattgacct gaaaaactgt gccagctaca 1260
aggagggtct gacttcagga aagtggttta aataacagtg caatttcaaa aaaatttata 1320
actttctttt gatcatcatg tacagagggt tttttttct ttaggcttct catgcatatg 1380
aatattttta gcacgaatgg actactaaat atctgagttt ttttttttt ttttttaaga 1440
tcttaacaga acatagcgta acaatatttg tcttccaggt gttactcatt tcaattatgt 1500
gtagtatacc aggacagacc tattttcatg tcttatttct ttaaagagct gcttcatlgg 1560
ccgggcgcga tggctcacgt ctgtaatccc agcactttgg taggctgagg tgggtagatc 1620

```

WO 00/56891

PCT/US00/07817

PF-0681 PCT

acctgaggtc aggagtttga gaccagcctg gccaacgtga tgaaattcca tctctacta 1679

<210> 53

<211> 1625

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2299506CB1

<400> 53

```

gcgcgtcccca ccttttagcga gaccaacgag agaacaccgc ctgcagctag aacagcctgg 60
tcaggagcgt aacggagtggt tgcgcacaac tgagaggaaa cccgtgcgcg gctgcgcttt 120
cctgtcccca agccgttcta gacgcgggaa aaatgctttc tgaaagcagc tcttttttga 180
aggggtgtgat gcttggaagc attttctgtg ctttgatcac tatgctagga cacattagga 240
ttgggtcatgg aaatagaatg caccaccatg agcatcatca cctacaagct cctaacaaag 300
aagatatctt gaaaatttca gaggatgagc gcatggagct cagtaagagc tttcgagtat 360
actgtattat ccttgtaaaa ccaaagatg tgagttcttg ggctgcagta aaggagactt 420
ggaccaaaca ctgtgacaaa gcagagttct tcagttctga aaatgttaaa gtglttgagt 480
caattaatat ggacacaaat gacatgtggt taatgatgag aaaagcctac aaatacgctt 540
ttgataagta tagagaccaa tacaactggt tcttccttgc acgccccact acgtttgcta 600
tcattgaaaa cctaaagtat tttttgttaa aaaaggatcc atcacagcct tttctatctag 660
gccacactat aaaatctgga gaccttgaat atgtgggtat ggaaggagga attgtcttaa 720
gtgtagaatc aatgaaaaga cttaacagcc ttctcaatat ccagaaaaag tgtcctgaac 780
agggagggat gatttgggaag atatctgaag ataaacagct agcagtttgc ctgaaatatg 840
ctggagtatt tgcagaaaat gcagaagatg ctgatggaaa agatgtattt aataccaaat 900
ctgttggtgt tttctattaa gaggcaatga cttatcacc ccaaccaggta gtagaaggct 960
gttggttcaga tatggctgtt acttttaaat gactgactcc aaatcagatg catgtgatga 1020
tgtatggggt ataccgcctt agggcatttg ggcataattt caatgatgca ttggttttct 1080
tacctccaaa tggttctgac aatgactgag aagtggtaga aaagcgtgaa tatgatcttt 1140
gtataggacg tgtgttgtca ttattttag tagtaactac atatccaata cagctgtatg 1200
tttctttttt ttttctaatt tgggtggcact ggtataacca cacattaaaag tcagtagtac 1260
atttttaaat gaggttggtt tttttcttta aaacacatga acattgtaaa tgtgttgtaa 1320
agaagtgttt taagaataat aattttgcaa ataaactatt tttttgctga ttggttaaaa 1380
aattctaat tatgaacatt agaaatctgt ggggcacata tttttgctga ttggttaaaa 1440
aatttttaaa ggtcttttagc gttctaatg atgcaaatga tatctctagt tgtgaatttg 1500
tgattaaagt aaaactttta gctgtgtggt ccctttactt ctaatactga tttatgttct 1560
aagcctcccc aagttccaat ggatttgcct tctcaaaatg tacaactaag caactaaaga 1620
taatt

```

<210> 54

<211> 1212

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2506558CB1

<400> 54

```

actggtcaag ttcaagtcac acaggtttgc tgactgcgcc atattgttgc tgacacaact 60
ggagactgga cttaggaatg tttttgccac acttaacaga tgtccaaaaa gactcctgac 120
tgctgagtca acagctcttt ataccacctt tgatcaaata ttggcaaaac acttgaatga 180
tggtaaaatc aatcagcttc ctcttttctt tggagagcct gctatggaat ttctctggga 240
tttctgaac catcaggagg gtccccgcac aagagatcat ttaagccacg gggagatcaa 300
cttacatgaa ttttcaaaag aaacaactaa tcagttgctt gcattttctc ttgtactgct 360
actcagattc gttgatgact gtctgctatc agtttttaag gaaaaatcag ccgtagaatt 420
gttgattagt cttgcagaag gctatagttc tcgctgtcat ccggtttttc agcttaaaaa 480
acaggtgctg agctgtgagg agagcatcag ggtttgggct ctgctgcctt tccccgaaga 540
actcactcgg caagccgtca gattagaaga taattctgaa acaaatgcct gccactcttt 600

```


WO 00/56891

PCT/US00/07817

PF-0681 PCT

```

ctttctgcaa acttggcctg attatggcat atttctatat gtgtgaccgt gcaaactctgt 240
tcatgaagga aaacaaattt tatacacatt catcttttctt tattccaatt atctacattt 300
tggttttggg agtattttat aatgaaaata ctaaagagac taaagtatta aatagagaac 360
aaacagacga atgggaaaggc tggatgcaac ttgtgatttt gatttatcac atttctggag 420
caagtacatt tttgcctgta tacatgcaca ttcgagttct gggtgctgca tatttatttc 480
agacagggtta tgggcatttc tcatactttt ggataaaagg agatttttggga atctatagag 540
tatgtcagggt tttattttcgt ctcaattttcc tggtagtggt gttatgtata gtaatggatc 600
gaccttatca attctattac tttgtccctt tggtcactgt atggttcatg gtcatatatg 660
ttacttttagc actatggcca caaataatcc aaaaaaaagc aaacggaaat tgtttctggc 720
atthttggctt actgttgaaa ctaggctttt tgcgtgttatt catatgtttt ttggcatatt 780
ctcagggtgac atttgagaag atctttttctc tttggccatt gtccaagtgt tttgaactga 840
aagggaatgt atatgaatgg tggttcagat ggaggttaga ccgttatgta gttttccacg 900
gaatgctgtt tgctttttatt tatctggctt tgcagaagcg tcaaataactt tctgaaggaa 960
aggggtgaacc tcttttttca aacaaaattt caaattttct gttgggttatt tcagtagttt 1020
ctttcctggg taagttttga aaacctttcc caaattctaa aatgggtatg ggaatattta 1080
accatttaag ataatggaaa atataaatcc aattattttt taataattaa atcctttttt 1140
tcctccctta tttttccctt ttaataattt

```

<210> 57
 <211> 1421
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4901066CB1

```

<400> 57
gaaccaggaa agtaacggct acagacagtg agaaatagtt tcgctcgccg gctagaaaaa 60
ctctgtcggt accaacccca gagcgttgag agcagcccac ctccacgctt ccttaacgga 120
gaggtgcagg actcagactt caccagccca ctccgtccca gccttgtacg caaagagacg 180
ccaaggacgc gctctcccg ctcaggcag cccagccttg ctggcttgcc tgcccgcctg 240
cgtgcagcac tcggccggcg tgcagcatga ccctgtggaa cggcgctactg cctttttacc 300
cccagcccg gcatgccgca ggcttcagcg ttccactgct catcgttatt ctagtgtttt 360
tggtcttagc agcaagcttc ctgctcatct tgccggggat ccgtggccac tcgcgctggg 420
tttggttggg gagagttctt ctcagctctgt tcataggcgc agaaattgtg gctgtgcact 480
tcagtgcaga atgggttcgt ggtacagtga acaccaacac atcctacaaa gccttcagcg 540
cagcgcgcgt tacagcccg gtccgtctgc tcgtgggcct ggagggcatt aatattacac 600
tcacagggac cccagtgcac cagctgaacg agaccattga ctacaacgag cagttcacct 660
ggcgtctgaa agagaattac gccgcggagt acgcgaacgc actggagaag gggctgccgg 720
accagtgct ctacctggcg gagaaagtca caccgagtag cccttgcggc ctgtaccacc 780
agtaccacct ggccgggacac tacgcctcgg ccacgctatg ggtggcgctc tgcttctggc 840
tcctctccaa cgtgctgctc tccacgcgg cccgctctca cggaggcctg gcactgctga 900
ccaccggagc cttcgcgctc ttcgggggtc tcgccttggc ctccatctct agcgtgccgc 960
tetgcccgt cgccttaggc tcctccgcgc tcaccactca gtacggcgcc gccttctggg 1020
tcacgetggc aaccggcgct ctgtgcctct tcctcggagg gccgtgggtg agtctccagt 1080
atgttcggcc cagcgcctct cgcacccttc tggaccaaag cgccaaggac tgcagccagg 1140
agagaggggg ctacactctt atcctcggcg accactgca caagcaggcc gctctccag 1200
acttaaaatg tatcaccact aacctgtgag ggggaccaa tctggactcc ttcccgcct 1260
tgggacatcg caggccggga agcagtgcgc gccaggcctg ggccaggaga gctccaggaa 1320
gggcactgag cgctgctggc gcgaggcctc ggacatccgc aggaccagg gaaagtctcc 1380
tggggcgatc tgtaataaaa cctttttttt ttttgttttt t

```

<210> 58
 <211> 2310
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 5031174CB1

WO 00/56891

PCT/US00/07817

PF-0681 PCT

```

<400> 58
ccggccctag gtccccggcag cgggtggtgac ggccgggtgccg gaggttggtcc ttggcagggtt 60
ttcctcggcg cttctccatg gaggaggcgg tgcgaacggc ttcagccccg aatgctcgca 120
tctcccactg gacggcgacg aaggcgggtg cegtgcgagc gcaggactgg gcggcctgtg 180
tgggggtgtg agccgcggtg cccaaggctg cgcggcgag ggggaagccgc gcgggccggcc 240
ggccgactag ggtttgaaga ctgcttcatt ctgctctag taccagcggg ttctctgttc 300
tgtgatcaat gtgattcaca ggaactcctt aagtaacaaa cgaaatgagc cagggggcgtg 360
gaaaaataga cttctatatt ggtctgggat tggctatgag ctccagcatt ttcattggag 420
gaagtttcat tttgaaaaaa aagggcctcc ttcgacttgc caggaaaggc tctatgagag 480
cagggtcaagg tggccatgca tatcttaagg aatgggtgtg gtgggctgga ctgctgtcaa 540
tgggagctgg tgagggtggc aacttcgctg cgtatgcgtt tgcaccagcc actctagtga 600
ctccactagg agctctcagc gtgctagtaa gtgccattct ttcttcatac tttctcaatg 660
aaagacttaa tcttcatggg aaaattgggt gtttgctaag tttcttagga tctacagtta 720
tggtcattca tgcctcaaag gaagaggaga ttgagacttt aaatgaaatg tctcacaagc 780
taggtgatcc aggttttgtg gtctttgcaa ccttgtgtgt catttgtggc ttgatattaa 840
tcttcgtgtg gggctcctgc catggacaga caaacattct tgtgtacata acaatctgct 900
ctgtaatcgg cgcgttttca gtctcctgtg tgaagggcct gggcattgct atcaaggagc 960
tgtttgcagg gaagcctgtg ctgcggcctc cctggccttg gattctgctg ctgagcctca 1020
tcgtctgtgt gaggcacacg attaattacc taaatagggc cctggatata ttcaacactt 1080
ccattgtgac tccaatatat tatgtattct ttacaacatc agttttaact tgttcagcta 1140
ttctttttaa ggagtggcaa gatatgcctg ttgacgatgt catttggtact ttgagtggct 1200
tctttacaat cattgtgggg atattcttgt tgcattgcct taaagacgtc agcttttagt 1260
tagcaagtct gcctgtgtct tttcgaaaag acgagaaaag aatgaatggc aatctctcta 1320
atatgtatga agttcttlaa aataatgaag aaagcttaac ctgtggaatc gaacaacaca 1380
ctggtgaaaa tgtctccga agaaatggaa atctgacagc tttttaagaa aggtgtaatt 1440
aaaggttaat ctgtgattgt tatgaagtga atttgaatat catcagaatg tgtctgaaaa 1500
aacattgtcc tcaaataatg ttcttttaag gcaatctttt taaagatttc actaatttgg 1560
accaagaaat tacttttctt gtattttaa acacaatggg agctcactaa aatgacctca 1620
gcacatgacg atttctatta acattttatt gttgtagaag tattttacat tttcatccct 1680
tctccaaaag ccgaatgcac taatgacagt ttaagtcta tgaaaatgct ttattttttc 1740
attggtgatg aaagtctgaa atgtgcattt gtcattccca ctccatcaat cctgaccat 1800
gtaaggcttt tttattttta aaaaacagag ttatcccaat acattatcct gtgatttacc 1860
ttacctacaa aagtggctcc tgtttgtttg atgatgattg gtttlatttt tgaaatattt 1920
attaagggaa aactaagtta ctgaatgaag gaacctcttt cttacaaaac aaaaaaaagg 1980
gcagaaatca cccaaggaa cgatttctca ggttgagatg atcacagtga atccggcttc 2040
ctctgagcat tcgatggcct tagcacctca tcaagccagc acatcctgcc tgctgttgca 2100
gcctggctgg gtttattctt cagttaccct aatcccatga tgccctggaac cttgattacc 2160
gttttacatc agctcttgta cttttcagta tattttcata atgagttata ttgtcattta 2220
gactttgaac agctctggga aatagaagac taggggtgtt tcttaaattt agctcatgtt 2280
ataataaaaa gttgcaaatt aaaaaaaaaa 2310

```